

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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DERMATOLOGIC AND OPHTHALMIC DRUGS

ADVISORY COMMITTEE 49th MEETING

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Friday, March 20, 1998

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Holiday Inn
 Walker Room
 2 Montgomery Village Avenue
 Gaithersburg, Maryland

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

COMMITTEE MEMBERS:

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

Joel Mindel, M.D.
William Rosenberg, M.D.
James S. Kilpatrick, Jr., Ph.D.
Lynn Drake, M.D.
Eva F. Simmons-O'Brien, M.D.
O. Fred Miller, III, M.D.
Henry W. Lim, M.D.

FDA PARTICIPANTS:

Michael Weintraub, M.D.
Jonathan Wilkin, M.D.
Hen-Sum Ko, M.D.
R. Srinivasan, Ph.D.
Liberio Marzella, M.D.
Karen Weiss, M.D.

SPECIAL GOVERNMENT EMPLOYEES, CONSULTANTS AND GUEST
SPEAKERS:

Eduardo Tschen, M.D.
John J. DiGiovanna, M.D.
Mark Lebwohl, M.D.
Robert Stern, M.D.

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P R O C E E D I N G S

CHAIRMAN MCGUIRE: If the Advisory Committee could be seated, I'll see if we have a quorum.

Good morning, everyone, and I would like to especially thank guests and advisors for attending this morning.

This is day two of Meeting 49 of the Dermatologic and Ophthalmic Drugs Advisory Committee for the FDA, and today we are going to consider questions regarding clinical trials for stable plaque psoriasis.

I would like to remind the committee that half of yesterday was a closed session, and we act like that never happened. We don't talk about any of that material today.

Tracy Riley, who is the 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 the financial interests reported by the committee participants, it has been determined that since the issues to be discussed by the committee will not have a unique impact on any particular firm or product but, rather, may have widespread implications to all similar products, in

1 accordance with U.S. Code 208(b) , general matters waivers
2 have been granted to the members and consultants
3 participating in today's meeting.

4 A copy of these waiver statements may be obtained
5 by submitting a written request to FDA's Freedom of
6 Information Office, Room 12A30 of the Parklawn Building.

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

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

17 Thank you.

18 CHAIRMAN MCGUIRE: Before we go to the open public
19 hearing, I would like members at the table to introduce
20 themselves. Mike Weintraub, FDA, is missing, Jon.

21 DR. WILKIN: Thank you for pointing that out to
22 me.

23 [Laughter.]

24 DR. WILKIN: I'm Jonathan Wilkin, Division of
25 Dermatologic and Dental Drug Products.

1 DR. KO: Hen-Sum Ko, Medical Officer, Division of
2 Dermatologic and Dental Drug Products.

3 DR. SRINIVASAN: R. Srinivasan, Team Leader,
4 Biostat Division of Dermatologic and Dental Drug Products.

5 DR. MINDEL: Joel Mindel, Departments of
6 Ophthalmology and Pharmacology, Mount Sinai Medical Center,
7 New York.

8 DR. SIMMONS-O'BRIEN: Eva Simmons-O'Brien,
9 Departments of Dermatology and Internal Medicine, Johns
10 Hopkins, Baltimore, Maryland.

11 DR. KILPATRICK: Jim Kilpatrick, Department of
12 Biostatistics, Medical College of Virginia, Richmond,
13 Virginia.

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

17 CHAIRMAN McGUIRE: Joe McGuire, Department of
18 Dermatology and Pediatrics, Stanford.

19 DR. DRAKE: Lynn Drake, Departments of Dermatology
20 at the University of Oklahoma Health Sciences Center and at
21 Massachusetts General Hospital in Boston.

22 DR. LIM: Henry Lim, Department of Dermatology,
23 Henry Ford Hospital, Detroit, Michigan.

24 DR. ROSENBERG: Bill Rosenberg, Dermatology,
25 University of Tennessee College of Medicine.

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

3 DR. MILLER: Fred Miller, Department of
4 Dermatology, Geisinger Clinic, Danville, Pennsylvania.

5 DR. DiGIOVANNA: John DiGiovanna, Department of
6 Dermatology, Brown University School of Medicine, and
7 National Institutes of Health.

8 DR. LEBWOHL: Mark Lebwohl, Department of
9 Dermatology, Mount Sinai, New York.

10 DR. STERN: Robert Stern, Department of
11 Dermatology, Beth Israel Deaconess Medical Center, Harvard
12 University.

13 CHAIRMAN McGUIRE: Thank you. As of this minute,
14 I don't have any participants for the open public hearing.
15 Has anyone been overlooked?

16 [No response.]

17 CHAIRMAN McGUIRE: Okay. Dr. Wilkin, are you
18 speaking for the FDA?

19 DR. WILKIN: I will.

20 Back in 1994, the Advisory Committee meeting in
21 September of that year focused on *onychomycosis*, and it was
22 not on a specific drug product. Instead, it was to define
23 what the indication really meant, what was a clinically
24 relevant endpoint that should be sought, and then different
25 kinds of microbiological studies that should be undertaken.

1 And we felt that was a very successful meeting. We got a
2 lot of important information, and you probably recognize
3 that quite a few drugs came in shortly thereafter. And we
4 used the committee's advice extensively in our thinking
5 about those products.

6 Similarly, today we are hoping for committee
7 advice on the endpoints of psoriasis, what are clinically
8 relevant endpoints, and some ancillary questions. The way
9 we have it organized is we have invited two experts in the
10 field to come and tell us about psoriasis. Dr. Robert Stern
11 from Harvard will give us an overview and approach the
12 notion of what patients might be seeking in their treatments
13 for psoriasis. Dr. Mark Lebwohl has participated, conducted
14 extensive studies, used different kinds of assessment tools
15 to assess severity of psoriasis, and he will speak to his
16 experience in that area. And they will stay at the table to
17 participate in the discussion.

18 We also have, of course, on the committee Dr. Bill
19 Rosenberg, who likewise is recognized as an expert in
20 psoriasis. So I think we are well resourced today to
21 approach these questions.

22 CHAIRMAN McGUIRE: Thank you, Dr. Wilkin.

23 Dr. Stern, it's yours.

24 DR. STERN: Thank you very much. It's a pleasure
25 to be invited here. This is a talk I haven't given before

1 because Dr. Wilkin's charge to me was to try to give an
2 overview of psoriasis, as he says, from what it is the
3 patient wants and how to measure it. And I will talk
4 essentially nothing about pathophysiology, and I will
5 concentrate pretty much on what was termed stable plaque
6 type psoriasis. But those of us who treat psoriasis know
7 that psoriasis is, in fact, a dynamic disorder, even the
8 stable plaque type form.

9 First, a little background. The first slide?

10 First, no epidemiologist can start talking about a
11 disease, and some of the most salient points about psoriasis
12 have to do with its commonness and its persistence. So in
13 the first slide you will see that the prevalence of
14 psoriasis is about 1.5 percent in the United States. So we
15 are talking about a disease that is very common, probably
16 three or four million affected individuals at any given time
17 in the United States. Most studies suggest that males and
18 females have about the same prevalence of psoriasis.

19 Is three or four million people a lot or a little?
20 One of the things that you have to recall about psoriasis is
21 that it is a disease that has onset that can begin from
22 infancy to the report that I have seen that the oldest is
23 108 years of age. But for most people, the most common
24 times for onset are, in fact, beginning in late adolescence
25 and through the 30s. So what this means, the average

1 individual who has psoriasis, who develops psoriasis, will
2 probably have that disease for about 50 years. So this is a
3 disease that is not a one-time factor, but, in fact, a
4 chronic factor.

5 On the other hand, in a given individual over
6 time, independent of therapy, the extent of the disease as
7 well as the extent to which the disease is increasing will
8 vary both for factors we understand and often because of
9 factors we have no concept of.

10 so psoriasis is, therefore, a chronic disease that
11 varies in severity over time in an individual, and one of
12 the problems, if you treat people with more severe
13 psoriasis, is early onset is associated with more severe
14 disease. And why is that important? Well, it's important
15 for a variety of reasons, as I will talk about in more
16 detail, for a disease that affects basically one--the
17 primary organ at which one looks in assessing other
18 individuals, young people are likely to be more affected by
19 changes in appearance than older people in terms of social
20 and psychological factors.

21 It affects individuals because, if you get it
22 early, it's really a problem that persists and persists, and
23 it's one thing to live with acute problems. Living with
24 chronic disfiguring diseases is often much more troublesome,
25 and also because we generally lack therapies without side

1 effects, that if you have to use treatments with potential
2 toxicity longer, that have cumulative toxicity, it's more
3 and more of a problem coming up with a good therapy.

4 Now , we should remember that one of the most
5 difficult charges to this committee is, even though as I
6 understand it we are supposed to think about measures for
7 stable plaque psoriasis, we have to remember that even
8 within the family of stable plaque psoriasis, not all
9 psoriasis is optimally treated or requires the same therapy.
10 It should depend on the burden of the disease in the
11 individual, what that individually affected patient wishes
12 is to accomplish, the aggressiveness of the disease, two
13 individuals with identical-seeming plaques at a given point
14 in time can have very different disease with respect to how
15 it's behaving; the risks of the treatment and also the risks
16 of the particular risk characteristics of the individual,
17 and because no treatment is without risk, the individual's
18 attitude towards the risk, how much are they willing to
19 trade off risk for benefit for their particular affliction.

20 So if we are making psoriasis better, since we are
21 not saving lives, we're not extending life span, what are we
22 trying to do? Well, in improving this disease, we're trying
23 to make disease feel better, the patient feel better, and
24 one generally, in looking at quality of life, tends to look
25 at three elements: physical, psychological, and social.

1 And let's talk a little bit about each of these elements as
2 it applies to psoriasis.

3 In the physical element, psoriasis affects daily
4 life in a variety of ways. First of all, I have mentioned
5 appearance. Secondly, it can lead to discomfort, itching.
6 Fissured and cracked plaques are quite uncomfortable,
7 stinging. Scaling is, to say the least, unpleasant. And,
8 of course, one of the things that bothers patients very most
9 is if they have plaques that bleed. And there are a number
10 of studies that show that people feel very stigmatized by
11 anything that leads to bleeding of plaques.

12 So these generally for stable plaque psoriasis--
13 I'm now not talking about erythrodermic or pustular
14 psoriasis, but for stable plaque psoriasis, basically
15 itching, pain, scaling, bleeding are the physical signs, and
16 to the extent to which the appearance of those cutaneous
17 alterations impact on their appearance or their perception
18 of their appearance is, of course, going to affect them
19 psychologically in terms of whether they feel physically and
20 sexually unattractive or they feel they've been made an
21 outcast. And there are a whole variety of studies using a
22 variety of quality-of-life measures that show that, in fact,
23 the physical decrements tend to be greatest for really large
24 areas of involvement, but it is the psychological factors
25 that are especially important in people who are young or

1 even middle-aged in terms of physical sexual attractiveness,
2 ability to make friends and to feel comfortable in social
3 situations. And the social, of course, is equally
4 important. People feel that it is more difficult to meet
5 people, to participate fully in family life because of their
6 appearances. You have a sort of dichotomy in terms of
7 relating to other members of your family with vacation: on
8 the one hand, a pull to going toward sunny places that might
9 help disease; on the other hand, many individuals being
10 unwilling to undress in those places because of their
11 concerns about their appearance and their impact on
12 individuals.

13 But it is certainly a disease that has been shown
14 to have substantial impact on individuals in all three
15 elements: physical, psychological and social. Quality-of-
16 life measures try to measure the impact of all three. Most
17 of the measures that have been used in clinical trials
18 really try to document various aspects of the first one of
19 these domains, the physical domain.

20 So when we think about burden, we can think about
21 the three domains and the physical features I have talked
22 about, but as I mentioned before, one must remember that in
23 any individual with a given type extent and distribution of
24 psoriasis, if you were to take a photo shot and take the
25 same patches of psoriasis from one photograph and put them

1 on a variety of other photographs and make that into people
2 who vary in age and gender and psychological status and
3 social and occupational status, and you then asked these
4 individuals who you've created identical psoriasis in, you
5 would find that the burden of that disease assessed by
6 reasonably robust measures would be extraordinarily
7 different and, further, the relief or the increase in
8 quality of life with treatment of the disease would also be
9 different.

10 One of the things I think we forget about with
11 psoriasis and its chronicity is that one of the factors that
12 affects treatment that we never--at least I'm not aware of
13 many evaluations--is that the frequency and need for
14 persistent therapy is really an extremely important aspect
15 in assessing quality of life or improvement of quality of
16 Life.

17 As I will elaborate on, patients who have only
18 temporary relief from signs and symptoms of psoriasis, who
19 anticipate or, in fact, experience rapid return of the
20 disease, find that the impact of these therapies are, at
21 best, modest .

22 Let me now talk a little bit about what matters in
23 terms of--other factors that matter in terms of the impact
24 of a given extent of disease.

25 First of all, location matters a lot. It matters

1 in terms of, as I have mentioned, the impact on the patient.
2 Clearly, psoriasis in some areas has much more of an effect
3 on social, psychological, or sexual functioning than other
4 areas. It turns out that even within stable plaque
5 psoriasis, at least in my experience, how easy it is to
6 clear different patches that look physically the same varies
7 with anatomic site. For example, some of the patches that
8 are hardest to clear often both patients least. Plaques on
9 the elbows, knees, and sacrum are often much more difficult
10 to clear than plaques just a few inches away on the lower
11 back, arms, and legs. And yet in terms of impact on the
12 patient, lower arm plaques or hand plaques are easier to
13 clear, but harder to--have much more effect on the patient.
14 And, of course, the importance of adverse effects, if there
15 local adverse effects, is going to vary according to the
16 location of the disease.

17 so, if we are going to be fair and we want
18 measurements of treatment response that are robust and
19 balanced, what do we need to control for? I have mentioned
20 about location of disease and how much the likelihood of
21 response varies according to location. The type of the
22 disease varies. The chances of response vary also.

23 Most scales basically tend to look at the
24 summation in some way of a variety of attributes that are
25 all co-correlated and, in fact, are not likely to be linear

1 in their response. So if you take erythema scale and
2 induration, or some people call it thickness, and you add up
3 these 0 to 3 or 0 to 4 scales, and you start with individual
4 plaques that have high numbers, that have all of those
5 attributes, substantial reductions in those attributes are
6 easy to accomplish. If you start with individual--and I
7 will illustrate this with some photographs in a few minutes.
8 If you start in general with thinner plaques, lower scores,
9 a comparable reduction in score is extremely difficult in
10 many cases to accomplish. So you can't compare clinical
11 study of thick scaly plaques, who are the patients of entry,
12 in terms of the percent improvement, with one that took
13 patients with comparable--in fact, greater extent of disease
14 but lower scores per plaque and say that these are--one
15 agent is better, the same, or worse than the other.

16 The other thing is it has been my observation that.
17 extent of disease matters, that not only--you have to
18 remember, psoriasis is a dynamic disease, and one of the
19 things I want to know as a clinician when I see someone, in
20 thinking about how aggressive to be in therapy, is I'd
21 really like a picture of what had been happening in the
22 previous weeks or months.

23 Clearly, it's easy to find out if you ask the
24 question whether a person's disease is just very rapidly
25 expanding even though it's still, to your eye, all plaque

1 psoriasis. But , really, a patient who has had essentially
2 the same plaques for long periods of time is likely to be
3 more treatment responsive than an individual who has had
4 slowly or moderately increasing plaque psoriasis, still what
5 would meet the definition of stable plaque psoriasis, but
6 it's on the upswing.

7 Similarly, it has been my experience that it is
8 much easier to effect change on an individual who has small
9 plaques of the same physical characters than large plaques.
10 It's not fair to compare a therapy and look at five plaques
11 this size rather than one plaque five times the size of that
12 and say, oh, look, these are doing the same, so the therapy
13 is equally effective. And it is also not only change in the
14 individual that is important, but, in fact, when an
15 individual has large areas affected, they probably have a
16 disease that is some way different in its biology and
17 responsiveness to therapy. So looking at individual plaques
18 in the context of large disease and seeing if you can clear
19 them is not the same as looking at individual plaques when
20 they are the only small individual plaques in terms of
21 responsiveness.

22 So I think you have to try to be sure that you are
23 looking at apples and apples when you say you are treating
24 plaques of a certain character in terms of what has been
25 happening with the patient, the size of the individual

1 lesions, the location of the lesions, and the overall
2 context is: Is this all the patient's psoriasis or is this,
3 in fact, just isolated plaques?

4 So these are some of the factors, I think, that
5 have to be controlled for if you are really trying to give
6 information that says where does this agent--how well does
7 this agent work, who does it work for, and if you're trying
8 to give information about, in a relative sense, how well
9 does it work compared to other standards.

10 Clinical patterns. Really, just for non-
11 dermatologists, I'm going to give a few slides and really
12 talk only about psoriasis vulgaris, guttate psoriasis, and
13 palmar/plantar, which some people would say would be plaque-
14 type psoriasis.

15 So this is your extremely typical elbow plaque,
16 pink to red, nice micaceous scale, extremely well
17 demarcated, absolutely typical psoriasis plaque. Elbows and
18 knees, often hard to clear, very easy to turn this plaque,
19 which is pink to red and quite scaly and quite raised, into
20 a very flat pink, non-scaly plaque. You can do that with a
21 whole variety of keratolytic and moisturizing agents pretty
22 easily.

23 This is thick plaque psoriasis, and, in fact, this
24 psoriasis is only moderately more difficult to clear because
25 this individual had been stable for a long time and

1 basically had reached a sort of steady state. Once you take
2 off the scale with basically keratolytics and you work on
3 the underlying inflammatory psoriasis, he responds
4 reasonably well to treatment. So a much higher score, not
5 that much more difficult to treat than the prior individual,
6 at least in my hands.

7 I'm sorry we can't see this, but this is a person
8 who has--in contrast, you can see extensive thin-plaque
9 psoriasis, including the lower legs, and clearly what would
10 make this individual feel better, reducing the score,
11 reducing the impact in this individual. They're already not
12 very scaly. They're not very thick. They are to this
13 person very disfiguring. This disease, to make it
14 substantially better from a patient's perspective, would be
15 much, much more difficult than the prior person's disease
16 is. And yet, by traditional scoring measures, the other
17 individual would have a huge decrement in score and
18 probably--whereas, this person, you'd probably have a higher
19 chance of getting any substantial decrement in score, and
20 even if you did, they'd probably not be very pleased with
21 it.

22 Guttate psoriasis. This is a type of psoriasis
23 that is eruptive, but one that's just there, it's stable.
24 Very, very treatment responsive. Treatment response to this
25 is not the same as treatment response to truly plaque

1 psoriasis, but if a person doesn't get therapy, this will be
2 around for months.

3 Palmar/plantar psoriasis. This is, I think by
4 definition, still plaque psoriasis. This disease is not
5 only obviously extremely disfiguring, interfering with every
6 kind of activity, painful, and, in fact, with non-systemic
7 medications, much more difficult to clear than even those
8 thickest plaques I illustrated earlier. And this is just
9 the other side of the hand, and you can see--you can imagine
10 the degree of morbidity associated with this condition.

11 Again, plantar psoriasis, extremely difficult to
12 clear, but yet in terms of a PASI score or in terms of most
13 other scores, if this is all this individual has, he might
14 be completely disabled in terms of if he has an occupation
15 that involves him being on his feet. Low score and very
16 hard to clear.

17 Location matters in terms of impact. Reasonably
18 hard to clear, especially in the hairline, not **very** much in
19 terms of overall extent, but quite disfiguring for this
20 individual if he is interested in social interactions.

21 so, again, coming back to my main theme: What do
22 patients want from psoriasis therapy? I have taken care of,
23 sometimes successfully, sometimes unsuccessfully, a lot of
24 patients over the last 25 years with psoriasis, and I have
25 tried to work with them on figuring out what it is that--

1 what's their endpoint? What is enough to make them better
2 or feel better about having spent the time to see me, spend
3 the money on therapy, and especially the time for many kinds
4 of therapies.

5 I think the minimum they want, uniformly--and,
6 again, this varies greatly with all the factors I have said,
7 individual to individual--is alleviation of symptoms. If
8 their psoriasis itches, hurts, bleeds, fissures, you need to
9 at least take that away. And any agent that reduces scores
10 and increases irritation and itching I'm not sure that that
11 agent, if it really induces inflammation or irritation or
12 soreness in plaques, is doing very much for patients. They
13 want the scale to be gone. Having scale constantly live
14 with you is both a--it's a social stigma. It creates family
15 problems. So at a very minimum, if you can't make it work
16 like normal skin in terms of not breaking, not itching, not
17 bleeding, and you can't make it from scaling, you probably--
18 no matter what you have done to a score, you have probably
19 not done very much for the great majority of patients I have
20 seen.

21 Next down the list is what they desire is many
22 patients, especially for disease that is on not usually
23 exposed areas, basically not on the face, not below the
24 sleeve on the arm, not on the neck, many patients with
25 disease, especially, in my experience, older patients, if

1 you can convert their psoriasis to red or pink macules that
2 are asymptomatic although there is still psoriasis there,
3 that is livable for them. People prefer normal looking
4 skin, normal feeling skin in terms of its texture, and that
5 skin really does not have quite the same texture--because it
6 is still psoriasis, it is just flat psoriasis--as hyper- or
7 hype-pigmented skin, which many treatments will leave either
8 as a result of the inflammation of the disease or a result
9 of the treatment. Patients will accept hyper- and hypo-
10 pigmented skin, especially if they think it will fade.

11 Of course, what they really want is normal skin.
12 Real psoriasis therapy is really a dichotomous variable. It
13 was there before. It's gone now in that place. And what
14 percentage of it is gone? To me, for truly effective
15 therapies, it is a very easy dichotomous variable.

16 Unfortunately, at least for topical therapies, we
17 don't have very many truly effective therapies, so we have
18 to look at other measures.

19 And another thing one has to emphasize is that
20 remission is important. This is a lifelong disease.
21 Patients want a treatment that, if they can reach normal
22 skin, without any substantial treatment, without at least,
23 with treatment that is far less than daily, they can
24 maintain normal skin over some reasonable period of time,
25 and I'll talk more about that.

1 So even an effective therapy, for example, UBG
2 phototherapy, that has to be used continually is not
3 acceptable to most patients with substantial disease. We
4 did some quality-of-life studies, and we were surprised that:
5 when we had patients on a whole variety of treatments--
6 methotrexate, PUVA(?) , UVB--and those who found the greatest
7 impact, controlling for extent of disease, were the UVB, the
8 ultra-violent B patients. Why? Because they required the
9 next frequent treatment. So it wasn't--their control was
10 excellent, but getting the treatment year after year was
11 driving them crazy. And so that's really not a truly
12 effective treatment for a disease that last, on average, 50
13 years.

14 Time to response is sort of the flip side of this
15 in terms of measuring effect. It has always seemed strange
16 to--until one thinks about one's own behavior, it always
17 seemed strange that I' ll have patients who come in who have
18 had untreated psoriasis that they haven't treated for months
19 or years, they have not had a sudden exacerbation, it's been
20 perking along, a little worse and a little worse, and they
21 have not done anything about it for 18 months, and they come
22 in and you describe the different treatments for the
23 disease, and you let them know it's going to take a month or
24 two before they're really substantially better, given the
25 way the treatments work, and that's entirely unacceptable.

1 When patients make a decision about pursuing, it's
2 just like that toothache that has been sort of there a
3 little bit for a long time, and then you finally decided,
4 even though it's not much worse, I got to see the dentist,
5 and the dentist says there's no appointment until next week,
6 you're furious. Well, patients with this chronic disease
7 have that exact same attitude, except they get to see the
8 doctor and then they want rapid response. And one of the
9 problems we have is that many of the agents we have take
10 weeks to a few months to be effective. So, certainly, from
11 a patient's standpoint, not only how long does it make it
12 better for once I stop using it, but how quickly does it get
13 me there, is an important clinical variable in the overall
14 effectiveness of the drug.

15 Let me just close, hopefully as a segue into Mark
16 Lebwohl's talk, about measurement scales for severity of
17 disease. I think they should be reasonable, reproducible,
18 and clinically meaningful. And they can be of a variety of
19 scales. I have sort of said that I really believe that the
20 best one is a nominal one. Basically you have plaques; they
21 either get better or they don't. It either looks like
22 normal skin or it doesn't, something easy to photograph.
23 That's when you have truly effective therapies. That's what
24 we've used as the percentage of body clearing with psoriasis
25 in UVB. It's measurable. You have to train people to

1 measure it properly or use photographs. Ordered is often
2 used. You know, how much better is it by a variety of
3 scales? Mark will talk much more about that.

4 I actually think for topical therapies, I think
5 ranked scales are, in fact, a potential way of looking at
6 these things, especially with good photographic standards.
7 However, I would suggest that when one evaluates agents, one
8 should not only, in a blinded fashion, compare before and
9 after photographs of agreed-upon areas and index plaques
10 with treatment and with placebo side by side, but one should
11 in time develop photographic standards that are such that
12 you can compare some of the standard therapies or have
13 three-arm studies so that with some of these agents you can
14 not only demonstrate that, yes, it had by these measures a
15 statistically significant effect compared to placebo, but
16 you can put the degree and types of changes, be they good
17 and bad, into the context of established agents for that
18 type of psoriasis. Again, here I'm talking about
19 established topical agents. Because I think when you try to
20 rate dispassionately old agent X versus new agent Y, and you
21 try to decide in which patients which one is better and is
22 the difference in cost justified, with the measures that
23 have been used, you don't have a clue. And what physicians
24 and patients really want to know is: Does the stuff that
25 costs \$2 a gram work any better than the stuff that costs 10

1 cents a gram? The only way to know that is really by well-
2 designed studies that give direct comparisons with robust
3 and accurate measures.

4 Let me then talk a little bit about something that
5 I have written about and talked about in the past, the PASI
6 score. As I have said before, it's the most popular
7 endpoint for improvement, so why not the PASI? Or as I like
8 to say, why we should pass on the PASI.

9 Well, first of all, the PASI is a copout in
10 studies of more severe psoriasis. It's a copout in
11 normalizing skin. You don't need a PASI score if you have a
12 truly effective therapy. You go from psoriasis to normal
13 skin. You don't need to quantify it.

14 What the PASI does through a weighting system that.
15 is, I believe, grossly at odds with good correlation with
16 things that are clinically important, it allows you to have
17 a scale that, in spite of its lack of reproducibility, gives
18 you ease at accomplishing significant changes in disease
19 that may not be clinically substantial. And let me
20 illustrate this.

21 The PASI score, for any who don't know, it's
22 basically--and there are more modifications of this
23 certainly than I have children. But they all involve
24 basically doing two things. They involve assessing a
25 variety of attributes of the individual plaque, most

1 classically redness, thickness, and degree of scale; doing
2 it separately, generally, on different anatomic areas,
3 weighting those according to their approximate total body
4 area; and then multiplying them by a factor of how much of
5 that body area is affected.

6 The problems with this is that improvement can be
7 substantial just by reducing scale or induration and a
8 little bit of erythema without coming close to even normal
9 looking skin. And equal scores or equal can represent very
10 different disease states, which I will illustrate in a
11 moment, and the improvement from equal scores can give you
12 very different clinical implications.

13 So let me--so here is a gentlemen who has these
14 plaques that I think you could argue are very scaly, very
15 thick, and, underneath, very red. So he gets a 12. And
16 let's say--I'm sorry. Let's say he has them not only here,
17 but he also has them on his elbows, and he also has a sacral
18 plaque, one of those lesions that often occurs, and he has
19 nothing on his face. His score would be just under 11,
20 about 10.8, under the traditional PASI system.

21 This individual has minimum scale, very thin
22 plaques, quite a bit of redness, less than 10 percent of
23 body area, and let's just say she also had sort of a
24 comparable percentage also on her legs and a few plaques on
25 her buttock. Her score would be about 6, about two-thirds

1 as much, making her substantially better, starting at this
2 point, even percentage-wise would be a therapeutic challenge
3 difficult to do with most of our topical therapies. You
4 could drop her scale score one. You might be able to make
5 her a little less red and indurated, so you might be able to
6 reduce her score perhaps 30 percent with topical therapies;
7 whereas, the prior gentleman, you should be able to get a 50
8 percent reduction or more just with a little emollient with
9 some alpha hydroxy acids in it.

10 So if the score for this person, who I would guess
11 would have substantial impact of the disease, is less and
12 improvement is harder than in the prior case, how can that
13 be a reasonable valid score which is transitive and
14 clinically meaningful?

15 Here is an individual who just has these plaques
16 on the dorsum of their hands. They're only pink. There's
17 no scale. Their PASI score is a fraction--if this is their
18 only involvement, is a fraction of 1. They have an almost
19 undetectable score. This person is disabled by their
20 disease, and making this disease better is going to be darn
21 hard. And it's dermatomyositis. It's psoriasis. So that's
22 another example of how little PASI reflects what's going on
23 with patients.

24 Another individual, clearly very diseased that's
25 going to highly affect the individual, not a very high PASI

1 score compared to our first, at least with topical agents,
2 very hard to clear, very hard to make much better because
3 there is no scale there. You can only start--in his case,
4 he's probably--in terms of his local area score, he's a 4,
5 and it's less than 10 percent of his head, so he's a 0.4 to
6 start. How much better can you be when you start at 0,4?
7 Yet lots of effect.

8 so, to conclude, I think that the primary
9 endpoints for truly effective treatment should be what most
10 patients want, that most originally involved skin becomes
11 norms 1, that there has to be a persistence of normality for
12 some decent interval after either stopping treatment or
13 decreasing the frequency of treatment to something that a
14 reasonable person would say is consistent with a normal
15 lifestyle. Whether that's a weekly treatment or a monthly
16 treatment and how long the duration is, I'm not sure, and
17 one would have to talk about it. But I think those are two
18 very important elements.

19 The secondary endpoints, still acceptable but need
20 better quantification, better agreed standards, and probably
21 need to be--we probably need to look more towards
22 photography and other imaging standards, and I don't mean
23 trans-epidermal water lost or doppler studies. I mean thing
24 that are clinically meaningful as opposed to biomechanically
25 quantified, looking for hyper- and hypo-pigmentation as

1 endpoints, macular erythema that persists and does not
2 immediately go on to thicker lesions, and at least therapies
3 that flatten and remove scale for persistent periods.

4 So I think it is possible to separate efficacy
5 assessment from cost and risk assessment, but any clinical
6 efficacy assessment has to consider as part of at least the
7 information that the clinician and patient should have,
8 which to me means it should be part of the label, is ease of
9 use, frequency of use, both with respect to the time it
10 takes per application and how many applications a week, and
11 also time to clearing, time to flare, and then some true
12 measures of true effectiveness, either primary or secondary
13 endpoints, and hopefully in the context of comparisons to
14 established agents advocated for similar extensive disease.

15 I thank you very much.

16 [Applause.]

17 CHAIRMAN MCGUIRE: Dr. Stern, I think if there are
18 any burning questions, we could have them now. I don't want
19 to have a prolonged discussion, but if anyone has anything
20 to ask Dr. Stern? Dr. Drake.

21 DR. DRAKE: Just a quick question. Can you tell
22 us what you think--if somebody can pull it up, what's the--
23 the quality-of-life stuff you did, is that with a validated
24 questionnaire, and is it published? I probably just
25 overlooked it, but could you give me your reference on that?

1 DR. STERN: We did a study within the PWA cohort
2 where we basically used a sickness impact profile and then
3 did our own psoriasis disability index, which we basically
4 constructed borrowing what we thought were the best elements
5 of a variety of other reasonably validated indices to look
6 at impact of disease. But , you know, there's a whole
7 variety of quality-of-life measures out there that are both
8 skin disease-generic--obviously they're generic measures--
9 skin disease-generic, like Skindex, and psoriasis-specific.

10 The problem with them is that impact is so--once
11 you've controlled for extent of disease, impact varies so
12 much according to sociodemographic features and duration of
13 disease. In fact, one of the discouraging things, if you're
14 someone who treats disease, is that except for individuals
15 with extraordinary amounts of disease, the amounts of
16 decrement in impact that one observes when one makes their
17 disease objectively much better is often very low, and it's
18 been my hypothesis, although I have not tested it, that that
19 in part reflects the fact that these patients know their
20 disease is going to be back, and in terms of the social and
21 psychological dimensions, it really hasn't alleviated it.
22 So the physical get better and the other two don't vary very
23 much even though they look much better.

24 DR. DRAKE: Thank you.

25 CHAIRMAN McGUIRE: Rob, thanks very much.

1 The next guest--Jon? Dr. Wilkin?

2 DR. WILKIN: Actually, I just wanted to clarify
3 one thing. In the past, if you look through the CFR, there
4 really is no provision for an active comparator that a
5 sponsor would have to compare their new product against.
6 And most recently, in the Reinventing Government, it's
7 actually had even a change from that in that if there is
8 already a product on the market, a new product does not have
9 to be as effective as a product on the market unless it's
10 for a life-threatening or severely debilitating disorder.

11 DR. STERN: Let me respond to that in two ways.

12 First, depending on the agency's ability to set up
13 photographic standards, it is possible with this disease to
14 essentially develop a library from other studies of
15 photographs that can be included in the evaluation set
16 without them being in part of the same trial. They're
17 really sort of your standards as long as people are blinded.

18 Secondly, it is true--I understand that in terms
19 of approval, but if you want--you know, one of the things
20 that is likely to happen, especially with cost containment,
21 companies may need to establish that their agent does
22 something at least as well or better than the comparator,
23 and that may be something where you can offer them, your
24 label can indicate that compared to agent X, the established
25 agent X, it was better in these ways, or didn't make it.

1 Because it's my impression that in terms of the commercial
2 viability of many products, if they can't--when they're
3 coming out at 10 to 50 times what the established product
4 costs per application, if they can't establish that they're
5 at least a little bit better, as fewer payers have more
6 control over what they'll pay for, they may not be
7 commercially viable.

8 I know those aren't agency things, but I think
9 there are a variety of interesting strategies that you can
10 use to make it in the sponsor's best interest to do those
11 studies, and so people really have the clinically important
12 information for that product.

13 CHAIRMAN McGUIRE: Okay. Our next guest speaker
14 is Mark Lebwohl.

xx 15 DR. LEBWOHL: Thank you very much. Let me have
16 the lights down, please.

17 Dr. Stern has set me up very well. I was charged
18 to review the methodologies that we use to evaluate
19 psoriasis, and actually you're going to save me some time
20 here. But just to review very quickly, PASI score, which is
21 one of the earliest attempts and certainly one of the
22 methodologies in most widespread use around the world to
23 evaluate psoriasis, involves looking at three parameters--
24 erythema, or redness; infiltration, of plaque thickness; and
25 desquamation, or scale--rating them on a 0 to 4 scale, and

1 then multiplying that by the area of involvement, and thus
2 you come up with a total body score for severity of
3 psoriasis.

4 Now , I agree entirely with Dr. Stern that we have
5 to pass on the PASI, and I will show you the flaws of this
6 particular methodology, and that it is in widespread use
7 just shows you that we have to improve the methodologies
8 that we have. But I'll show you others that are currently
9 in use as well.

10 This is a theme that Dr. Stern built upon, and
11 that is, here is a patient with terrible psoriasis, and this
12 would not get a score of 12, which is the maximum severity
13 score, if you add up a 4 for redness, a 4 for thickness, and
14 a 4 for scale, because there's very little scale here. This
15 patient would get an 8 or maybe a 9 if you gave her a 1 for
16 scale, and yet this is as bad--and, in fact, she wouldn't
17 even get a 4 for plaque thickness. Yet this is certainly
18 severe psoriasis.

19 There are many other reasons why investigators do
20 not like using the PASI score. First, it's very tedious,
21 and it is fraught with inaccuracies. And I'm going to just
22 point out some of the flaws of the PASI in the context of a
23 mini-study that we did. And we did this at two time
24 intervals separated by six months. We used the same three
25 judges--this happened around Olympic time--and they rated

1 each of these parameters, and we only did isolated body
2 sites . So we didn't do a full PASI score. And let me show
3 you what we came up with.

4 Here's the first photograph we showed at the
5 beginning of the six-month interval, and we showed it to the
6 three judges, and they were very uniform. This is pretty
7 bad psoriasis, and they all rated this patient as severe
8 across the board, minor discrepancy in the area of
9 Involvement . This is 70 to 89 percent. This is 50 to 69
10 percent. But other than that minor discrepancy, very
11 uniform agreement that this is a terribly affected patient.

12 We then showed them this photograph, and this is
13 pretty bad as well, and this patient was rated, when you add
14 up erythema, infiltration, and desquamation, anywhere from 4
15 to 6, average of 5 by the three judges, all pretty close.

16 Six months later, we went back to them and we
17 didn't show them the first patient. We only showed them the
18 second patient. And not having that first patient, the one
19 who came in in the morning and had psoriasis so severe that
20 everybody else the rest of the day had it mildly. So not
21 showing them that first patient, the same three judges six
22 months later--and, incidentally, we had a photographic
23 standard that Dr. Stern suggested, which I agree with
24 completely. It helps a lot to have standard photos for how
25 you should rate the various parameters.

1 Here are the scores. It averaged 5, if you
2 remember, before. Here the lowest score added up to 6 and
3 the highest to 10. So a dramatic difference in the score
4 depending on who they saw earlier that day. One critical
5 flaw in the PASI score.

6 Now, this is a patient that I certainly would call
7 erythrodermic. The judges--and I would not use a PASI score
8 to rate that, and the reason I wouldn't is for exactly what
9 you see here. The judges thought this was severe in all
10 parameters, but, you know, it's true that plaque thickness,
11 the severity ranges from 1, minimal, to 4, very severe. So
12 that that is an area where the PASI certainly is not useful.

13 And guttate psoriasis, in our clinical trials we
14 generally look at plaque psoriasis, but everyone knows that
15 many patients with plaque psoriasis will have guttate
16 lesions. Right next to that plaque you have lots of little
17 tiny spots. And the obvious area of disagreement here is
18 the area of involvement. Is this 100 percent involvement?
19 Is this 50 percent? Is it 10 percent?

20 There was general agreement in the scores except
21 on the area of involvement, which ranged from a low of 3,
22 which is 30 to 49 percent, to a high of 5, which is 70 to 89
23 percent, so as much as a 40 percent difference in the area
24 of involvement as judged by the investigators.

25 So the PASI is certainly fraught with difficulty

1 not only on a judge versus judge, an inter-individual
2 variation, but even within the same investigator at
3 different time points in the same patient.

4 Now , what's wrong with this patient who comes in
5 and evaluated by a PASI score? Well, other than the fact
6 that it's out of focus, what's wrong with this patient is
7 this is one plaque. This is the only plaque the patient
8 has. One percent of the body surface area is the palm of
9 the hand. So this is about 1 percent. This patient would
10 have a maximum PASI score of 1.8 or certainly less than 2,
11 and yet this is a fairly bad plaque, but it is the only
12 plaque.

13 You would be foolish to use a PASI score to
14 evaluate a patient with very limited psoriasis. This score
15 simply is not going to reflect the endpoints that you're
16 looking for in terms of improvement of the disease severity.

17 Now , it turns out that there are many grading
18 scales, and they have in common the evaluation of scaling,
19 erythema, and plaque thickness. And they have different
20 scales. This one is a 0 to 8 scale. There are others that
21 are 0 to 3. I'll show you another 0 to 4. But the point is
22 that they have multiple steps at which you can differentiate
23 these three parameters, and they are pretty good at doing
24 that. But you have to keep your endpoints in mind.

25 This one looks at scaling, with 0 being no scaling

1 and going all the way up to very severe coarse, thick scales
2 as an 8, and gradations in the middle. Erythema, ranging
3 from no erythema to light red, to extreme red coloration.
4 Plaque thickness being absent or slight, going to moderate,
5 marked, and very marked elevation with hard, sharp edges.

6 And all of these are similar in the way they
7 approach it. The 0 to 3 has half points between it so that
8 there are seven points on the 0 to 3 scale; the 0 to 8 has
9 nine points. But they're all pretty similar in the way they
10 look at psoriasis.

11 In addition to that addition of those three
12 parameters is a scale of overall disease severity, and this
13 one can be fairly tricky. For example, in this particular
14 scale, 0 is no evidence of disease, 2 is mild, with
15 approximately 5 percent involvement, with an average plaque
16 elevation of 4, which is moderate plaque thickness and
17 scaling and erythema in a range of 2 was the definition
18 given here. Very severe is defined as 50 percent
19 involvement, with an average plaque elevation in the 6 to 8
20 range, and scaling and erythema in the 6 to 8 range.

21 Well, what if you have a patient who started out
22 with 50 percent involvement and 6 to 8 scores, and after two
23 weeks had 50 percent involvement and 1 to 2 scores? Is that
24 not a dramatic response? That person will still have 50
25 percent involvement.

1 Fortunately, in this scale, there is room for the
2 investigator to essentially put his opinion of the outcome
3 of the patient, because there is no 50 percent with scores
4 of 1 and 2 in the scale. So I would probably have ranked
5 that patient as mild even though the patient still had 50
6 percent--or maybe a little over mild even though the patient
7 still had 50 percent body surface area involvement.

8 'The single most useful score, I believe, is the
9 physician and the patient's global assessment. What's the
10 percentage of improvement? Because that way you can take
11 all the parameters into account and on this particular
12 scale, which is similar to all of the ones that are out
13 there, moderate improvement was judged as 50 percent, slight
14 improvement 25 percent, marked improvement 75 percent, and
15 then almost clear 90, and completely clear 100. So that is
16 a very useful way of evaluating benefit in psoriasis.

17 These are just other scales that are similar.
18 This is a 0 to 4 scale, and it looks at not only one target
19 site, but as Dr. Stern mentioned, it is much easier to treat
20 some areas than others, and so they artificially separated
21 out elbows and knees as being tougher-to-treat sites versus
22 non-elbow, trunk, arm, or leg, and then looked at all
23 treated sites as well. And they did the same thing with
24 erythema, plaque elevation, scaling, that I have shown you
25 before, only this time on a 0 to 4 scale. So there are only

1 Eive points here.

2 Again, they had very similar overall lesion
3 assessment and global evaluations, which they call here
4 response to treatment, with marked being 75 percent. And
5 we'll get back to that 75 percent number shortly.

6 There were several questions I was asked to
7 address in the course of this session. One of them is:
8 Should there be a minimum severity when evaluating products
9 for psoriasis? And the answer is of course. This is a
10 patient who has very mild psoriasis on a limb, and if you
11 simply put petrolatum on here, you can probably eliminate
12 most of this. So obviously there has to be a minimum
13 severity. And, traditionally, moderate plaque thickness is
14 the minimum requirement for entry into a psoriasis.trial,
15 and that doesn't allow you to enroll a patient such as this.
16 You really have to have more than this.

17 The next question I was asked is: Should there be
18 a minimum area of involvement? And I'm not sure that there
19 should be. This is a patient who has less than 1 percent
20 body surface area in this photograph, and there are patients
21 whose psoriasis is bad but limited to localized body sites.
22 And you can certainly judge very well whether a drug will be
23 effective on this plaque of psoriasis on the elbow, even
24 though it's less than 1 percent body surface area.

25 The next question I was asked to address is:

1 Should there be a relative importance assigned to the
2 different parameters: scaling, redness, and plaque
3 thickness? And this is a photograph I borrowed from an
4 atlas, and the point of this photograph is that you can take
5 comparable plaques, and simply by putting emollients on
6 them, you can eliminate all the scale. So that a third of
7 your score is then eliminated. Scale is not a good
8 endpoint. In fact, it's the one that really skews the PASI.
9 The patient who puts on vehicle in the PASI can drop by a
10 third, so that there are striking differences between the
11 three parameters, and some clinical trials will separate out
12 as an endpoint responsive plaque, plaque thickness. And
13 that is not an unreasonable endpoint.

14 Now, having separated these out, the next question
15 I was asked is: What about establishing dichotomous
16 endpoints? Instead of having an addition of scaling, plaque
17 thickness, and erythema, adding up all those parameters, why
18 not look at two different endpoints? One of them might be
19 just plaque thickness. One of them might be a skewed
20 addition of scaling, erythema, and plaque thickness. The
21 best one, in my mind, is the global evaluation, and what I'm
22 going to show you now are a series of slides in which
23 topical preparation was used, and I would say that when two
24 people see the same disease over and over again, they
25 usually will agree on 95 to 99 percent of what they see.

1 And the 1 percent that is--the only thing that I would
2 disagree with what Dr. Stern said is there are patients--and
3 it's a select group of patients. It will be patients who
4 have 10 to 20 percent body surface area. You know, some of
5 them just will not put up with that and they want to get rid
6 of it no matter what the cost, and others don't want to put
7 up with it but they don't want to come in for phototherapy
8 three times a week. And those patients, if given a **choice**.
9 of coming in for phototherapy for three months and then
10 staying clear for a period of months afterward, versus
11 putting on topical medications regularly in order to keep
12 their psoriasis away, there is certainly a group of those
13 **who** will much more readily put on the topical medications
14 than come in three times a week for phototherapy for three
15 months.

16 This was a study that addressed precisely that,
17 and without telling you the agents, I just want to show you
18 that when a treatment works, it can work for all the
19 parameters. And many of the treatments that we use do work
20 for all the parameters. This looked at scaling, and you can
21 see the vehicle group strikingly different from the active
22 treatment group. This is actually a combination of two
23 treatments, I should say, and it was one treatment versus
24 two. And you can see the group that got both treatments
25 versus the treatment plus vehicle was significant throughout

1 the course of study. Erythema was significant. Plaque
2 thickness was very significant. The overall evaluation was
3 significant. And the global response was significant.

4 So that many of our studies that improve two
5 parameters of psoriasis or three parameters will end up
6 improving every parameter that you look at.

7 The next point I was asked to discuss was
8 endpoints, and the picture that you see here is a patient
9 who received, again, two treatments on one leg, one
10 treatment on the other. He improved dramatically on both.
11 This leg took about two weeks longer to respond completely
12 than this leg. One of the treatments on this leg--this was
13 a combination of UVB and anthralin--was an absolute mess,
14 and he was very happy to wait the extra two weeks and judged
15 this side as better because he would certainly prefer to
16 live the rest of his life going for phototherapy two weeks
17 longer to get a six-month remission than to put on
18 anthralin, which is fairly messy, and go for phototherapy.
19 So there's a lot of patient variation in terms of what
20 they'll be willing to accept in terms of their therapy. So
21 that when you look at endpoints, you have to look at what
22 patients are satisfied with. Ideally, of course, complete
23 clearing is a wonderful endpoint. But know that many of the
24 treatments that we have will not achieve that endpoint.
25 Many of the treatments that we have will achieve 75 percent

1 improvement . Is that a treatment we should skip? Probably
2 nest patients would say no.

3 Now , the question then is what degree of clearing
4 or what degree of improvement is viewed by patients as
5 acceptable. And what I'm going to show you now are two
6 slides, and I have drawn them in my own handwriting so as to
7 eliminate the product name, but these are both published in
8 the last few years, and one of them has treatment success
9 defined as 50 percent or greater improvement. But it
10 doesn't say it on the graph. And they follow patients out,
11 and they achieve--with their active drug, about 70 percent
12 of patients achieve treatment success. But , again,
13 treatment success is only 50 percent or greater improvement.
14 Many patients will not be satisfied with that degree of
15 improvement.

16 This is another product, similar study, and the
17 graph looks virtually identical. About 70 percent of
18 patients achieve treatment success. But when you go back
19 and look at the manuscript, treatment success is defined
20 here as 75 percent improvement. When the drug has come out
21 into the marketplace, there is no contest in terms of
22 physician or patient perceptions as to which drug is
23 superior. The one that achieved 75 percent improvement will
24 do much better by patient preferences and by physician
25 preferences than the one that achieved 50 percent

1 improvement . Yet looking at the graphs, you could
2 practically put one on top of the other. So the endpoint
3 has to be defined, and it should be the same for all drugs.
4 And I would vote for 75 percent as being an endpoint that
5 should be achieved.

6 The next discussion that I was asked to address
7 was : Should it be a target area or should it be all sites,
8 or should the total area of involvement be involved? The
9 one advantage the PASI score has over other parameters that
10 we use is that the PASI addresses area, total area of
11 involvement. There are, of course, patients who don't care
12 if their shoulders are involved because their shoulders are
13 covered, but they do care a lot if their arms are involved.
14 And this patient actually simply would not treat her
15 shoulders. It simply didn't bother her at all. She wanted
16 her arms to be cleared, and that was the only site that she
17 treated.

18 A very important point that Dr. Stern addressed
19 was different sites of involvement respond very differently
20 to treatment. And, in fact, you can separate out
21 intertriginous sites and the face. Intertriginous sites are
22 sites where skin rubs against skin such as the axilla, the
23 groin, even the antecubital fossa. And those sites respond
24 very quickly. This is before, and this is after a few days
25 with a mild topical steroid--not mild. It's actually a

1 Class II topical steroid.

2 This is before, and this is, again, after just a
3 few days with the topical steroid.

4 Now , we know that the shin--you can put a topical
5 steroid on for 10 years, and you won't get that degree of
6 improvement . The shin is much more difficult to treat than
7 intertriginous sites.

8 Okay. We showed this actually several years ago.
9 We looked at intertriginous sites versus other body sites,
10 and actually, the face is another area that responds very
11 easily, and I'm sorry that this is difficult to see. But
12 this is treatment of psoriasis on the face or intertriginous
13 areas, and this is treatment of psoriasis in non-
14 intertriginous sites. You see a striking difference between
15 the two lines. The face and intertriginous areas respond
16 much more quickly.

17 Okay. This was put in because I was asked to
18 address quality-of-life issues, and this is a rectal
19 morphine sulfate, and the caption, which isn't visible,
20 says, "Why is this woman smiling?" I didn't put this in.

21 Quality-of-life issues in psoriasis are real.
22 There are many indexes that have been used to look at them,
23 and if you look at the multiple publications on quality of
24 life in psoriasis that have come out and you look at all of
25 the surveys that have been taken, the outcome in survey by

1 survey is different, with one exception, and that is that
2 nest of them fail to show a response to treatment. In other
3 words, the survey usually does not change with treatment

4 One of the problems that was shown recently in a
5 survey is that the stress of anticipating a negative
6 response from others contributes more than any to a
7 patient's quality of life and disability. And that is
8 something that is difficult to change unless you have a
9 treatment that gets rid of psoriasis and gets rid of it for
10 a long time. And, unfortunately, we don't have anything
11 that works quite so well.

12 The various indexes that are out there are all
13 very good at assessing quality of life in psoriasis, but
14 they, again, do not distinguish the benefits of therapy
15 reliably. There is a psoriasis life stress inventory.
16 There is a psoriasis disability index. There are some
17 generic indices. One is called Skindex, which looks at
18 quality of life with skin diseases in general. There are
19 other general health index. SF-36 is one that is widely
20 used.

21 None of them are perfect for psoriasis, but one
22 thing that comes out of each one of them is that the
23 patients' comments, when they look at those questionnaires
24 or surveys, are different from patient to patient. But if
25 you can separate out the patients' comments, they are quite

1 striking in terms of the disabilities that patients suffer.

2 This patient has no trouble with sexual relations
3 even though he' s covered head to toe with psoriasis. But he
4 can't wear anything that is white because his skin cracks
5 and he bleeds all over himself. That's his main disability
6 from psoriasis. Yet another individual will be embarrassed
7 in front of his or her spouse because of psoriasis.

8 So more comes out from the comments with these
9 questionnaires than from anything else. And there are
10 questionnaires that are very good at eliciting those kinds
11 of comments from patients. But as far as the efficacy of
12 therapy, so far we have not been able to get rid of that
13 anticipation, the stress of anticipating other people's
14 negative response. Because even if your psoriasis is gone
15 temporarily, you don't know when it will be back. And that
16 question remains unchanged unless you have a treatment that
17 is long term.

18 I think that is my last slide. Thank you very
19 much .

20 [Applause.]

21 CHAIRMAN McGUIRE: Mark, if you don't mind, could
22 you wait just a minute and let's see if we have a few
23 questions. Would anyone from the Advisory Committee like to
24 pose a question? Dr. Rosenberg.

25 DR. ROSENBERG: I think I could pose a question to

1 both of the speakers. Would you comment on relative
2 expect at ions and differences in evaluation of topical versus
3 systemic therapy?

4 DR. LEBWOHL: Yes. From a patient's point of
5 view, once they are ingesting something or getting it by
6 injection, they expect a greater outcome. Whether it's true
7 or not, regardless of the absorption of topical
8 preparations, they view that as being, in quotes, a stronger
9 therapy and expect more of it.

10 I think that is one of the reasons that some
11 agents like sulfasalazine, which has been shown to be
12 beneficial in a small proportion of patients, has not been
13 successful . It only offers limited efficacy to about 30
14 percent of patients in published clinical trials, has a
15 significant occurrence of not life-threatening, by and
16 large, side effects. But once patients are taking a pill by
17 mouth, they expect it to work. Now, you do achieve dramatic
18 results with oral cyclosporin, with oral methotrexate. But.
19 patients are often reluctant to take those therapies because
20 of concern over the side effects of those therapies.

21 As far as topical therapies, patients perceive
22 those as being less harmful. They're willing to accept less
23 benefit from topical therapies, I believe. But, you know,
24 especially with the cost of some of the topical therapies
25 that are out there today, a 100-gram tube of one of the

1 newer topical therapies sells for \$270 in Manhattan. If
2 patients spend \$270, they expect to get better, even if
3 they're getting it back from an insurance company.

4 And so there is a real disappointment when they
5 look at the price and put that on and it doesn't work.

6 Certainly everybody wants to be clear. Normal
7 skin is the most desired outcome, but there are plenty of
8 people who will be happy to use a topical therapy and get
9 almost normal skin or 75 percent improvement just with a
10 topical therapy, and they wouldn't say the same about a
11 pill. If they take a pill, they want 100 percent
12 improvement.

13 CHAIRMAN MCGUIRE: Dr. Drake?

14 DR. DRAKE: This is to both of you guys. I
15 appreciate your comments both on the quality of life--that,
16 you know, I think it's very hard to impact quality of life
17 with patients with psoriasis because of the expectation of
18 return of disease. But I want to ask you another question
19 that sort of relates to that, and I think they're all
20 interrelated.

21 I have seen patients with psoriasis be willing to
22 take on exceptional risk, and by exceptional risk, I mean
23 taking on drugs that are extraordinarily--have the potential
24 for extraordinary toxicity for basically what--I want to say
25 a benign disease. It's not benign in the overall scheme of

1 things, but it might be benign with respect to killing them.
2 All right? But they will take--they are actually very
3 willing, it seems, to take drugs that are potentially life-
4 threatening, the drugs themselves, and the disease is
5 probably not--in other words, I guess what I'm trying to ask
6 is: In more than any other group in clinical studies,
7 patients with psoriasis are very eager to volunteer; they're
8 very willing to be in high-risk studies.

9 Why do you think that is? Why do you think
10 they're more willing than patients with other disease to
11 undertake high risk? When you look at consent forms,
12 psoriasis patients almost never say no. They're almost
13 always willing to do it. Whereas, with other diseases,
14 they'll read the consent form, and if it's a high risk,
15 often they'll back away from it. And maybe that's only just
16 in my limited experience, but that's my sense of it. Is
17 that an accurate sense? And if so, why do you think that
18 is?

19 DR. LEBWOHL: I agree with you completely. It may
20 be the group of patients who come for clinical trials are
21 among that group who are really so bothered by their
22 diseases that they'll try anything. Certainly there are
23 patients who, you know, ignore their psoriasis and have very
24 little psoriasis, and it may be a high proportion of
25 psoriasis patients in the nation who have minor plaques on

1 the elbows, for example, and to them, you know, they don't
2 really have psoriasis. They don't even acknowledge that
3 they have psoriasis even though you've told them they do.
4 and they are the ones who have come to you for something
5 else, and you happen to notice it in the office.

6 But the ones who come to you for psoriasis are
7 obviously bothered by it, and very often what has come out
8 of a lot of these quality-of-life questionnaires is their
9 perception that other people are looking at them in a
10 negative way, is one of the most troubling aspects of this
11 to them. And I agree with you, you are absolutely right,
12 they will put them through unbelievable torment to get rid
13 of their psoriasis, and not just with drug studies, with the
14 approved drugs.

15 CHAIRMAN McGUIRE: Mark, it occurs to me that part
16 of our difficulty is semantic and the way we use the
17 language. If you think of a child with varicella, the child
18 may have 80 percent body involvement, but the 80 percent
19 that is involved by area is only 5 percent lesional.

20 DR. LEBWOHL: That is correct, yes.

21 CHAIRMAN McGUIRE: And that's the issue that
22 arises with guttate psoriasis, and you would say, well, we
23 have--the trunk is involved with guttate psoriasis, so
24 that's 40 percent of the body area, but, in fact, there are
25 2 percent lesional skin.

1 DR. LEBWOHL: Right .

2 CHAIRMAN MCGUIRE: That was one observation.

3 The other observation is that--I can't remember
4 whose comment this is, but if I hadn't believed it, I would
5 not have seen it, and--referring to the patient you showed
6 with the large pre-sacral and truncal very heavily scaled
7 lesions. Well, actually, there wasn't much erythema
8 showing.

9 DR. LEBWOHL: Right, but it's under that scale.
10 Everybody rated it as 4, actually.

11 CHAIRMAN MCGUIRE: That's right. But you graded
12 it as 4 because you knew what was underneath.

13 DR. LEBWOHL: Right .

14 CHAIRMAN MCGUIRE: If you had been a seventh
15 grader, you would have said there wasn't erythema.

16 DR. LEBWOHL: Right.

17 CHAIRMAN MCGUIRE: But you're a professional, and
18 you said, "I know what's under there. " But , in fact, that
19 is an imprecision in our measurement.

20 The other part of that is when you remove scale,
21 then the erythema value should go up because you can see
22 things that you didn't see when the scale was there.

23 DR. LEBWOHL: That's right.

24 CHAIRMAN MCGUIRE: We've done some funny things to
25 ourselves in this grading business.

1 DR. LEBWOHL: Sure. I have to tell you that the
2 photos that we used as standards had a photo similar to that
3 and did not rank erythema as a 4, but the investigators all
4 ranked it as 4. And I think that they--you know, I would
5 have agreed with them.

6 CHAIRMAN McGUIRE: Yes, Dr. Kilpatrick?

7 DR. KILPATRICK: These questions are a little bit
8 off the endpoint question, but may be of interest. Is there
9 a psychosomatic component in psoriasis? Is it ethical to
10 have a placebo arm treatment? And do we need blinding in
11 controlled clinical trials?

12 DR. LEBWOHL: Well, certainly, I believe it is
13 ethical to have a placebo arm in this because it is not a
14 life-threatening disease. One of the promises that we make
15 to our patients at the end of a clinical study, which, you
16 know, could even be incorporated into requirements if you so
17 deemed, is that we feel obligated to treat the patient
18 afterward. And at our site we always do.

19 But to answer your question, because it's not a
20 life-threatening disease, I don't see a problem with having
21 a placebo controlled side. The other question is: Do you
22 really need a placebo control? And the answer is you
23 certainly do. There's a big placebo response, especially
24 when you look at scaling. You can get rid of a third of
25 your scores if you use just those scores for endpoints by

1 getting rid of scale, and you can do that with Vaseline.

2 So this is a disease where you definitely need a
3 placebo group.

4 CHAIRMAN MCGUIRE: Rob, did you want to comment?

5 DR. STERN: A couple of comments. I think it
6 depends what your endpoint is. If, in fact, your endpoint
7 is complete normalization of individuals' skin who have
8 substantial involvement, you really don't need placebo if
9 you can control for external factors like sun exposure. I
10 would not accept those as Phase III trials, and I am not
11 advocating those. But I think if I were the agency and I
12 were looking at someone's Phase II(a) or II(b) protocol in
13 terms of sort of priority and they came in at that stage and
14 showed me photographs before and after of people who were
15 obviously not just additionally tanned, who had substantial
16 disease and their skin looked normal, that degree of
17 efficacy you don't need placebos to realize that you have
18 something that really works.

19 I think for the reasons Mark said, there should
20 still be placebo controlled trials, but, for example, I
21 might well design them with a much heavier load of patients
22 getting active drug in randomization relative to placebo. I
23 think for anything short of that, you absolutely need
24 placebo, and I think for a lot of these topical products
25 that are coming along, if you want to know whether it works

1 and whether it really has any pharmaco-economic, social
2 utility, you, in fact, need more than the placebo because of
3 our inability to really measure the clinical usefulness of
4 the drug in an understandable sense.

5 Getting back to Lynn's question, I think first of
6 all what we see in our practices where we see either
7 patients with--a disproportionate number of patients with
8 severe psoriasis, and especially when clinical investigation
9 is involved, you have a real biased ascertainment in terms
10 of not only the characteristics of the disease but the
11 personalities of the individuals that aren't necessarily
12 representative of the general population's attitudes toward
13 risk. So I think we have to be very careful about--while
14 people of similar severity and similar point in their
15 disease, et cetera, et cetera, probably would respond
16 comfortably, I think one of the things that's often missing
17 is if a drug that has some potential for toxicity is shown
18 to be sort of acceptable within the context of clinical
19 trials from a toxicity point of view, there may be the
20 assumption by the agency or by clinicians that this would be
21 generally acceptable to patients as a risk/benefit ratio
22 kind of--well, they knew what they were getting into, they
23 saw what happened, and they still wanted to use it. And
24 certainly I think your point is an excellent one. That may
25 not be representative of the larger population of patients

1 who didn't have these particular attitudes towards their
2 disease, particularly either risk takers or innovators, and
3 we have to be very careful about believing that, as people
4 have voted with their feet as part of clinical trials to
5 accept these kinds of risks, that other patients will
6 understand or be willing to accept those risks unless
7 they're very well spelled out.

8 CHAIRMAN McGUIRE: Dr. Rosenberg? And then after
9 Dr. Rosenberg's question or comment, we will go on to the
10 FDA presentation.

11 DR. ROSENBERG: I, of course, appreciate what Dr.
12 Wilkin said about product approval does not require a
13 comparison or really--not only not requires, but should not.
14 depend on comparisons with previously available or presently
15 available agents, nor necessarily, I guess it follows from
16 that, should the standards required for approval of new
17 agents be higher than those previously. And yet both
18 speakers I think made such an important point when they
19 talked about the time to relapse, how long does the patient
20 stay well. And certainly we know of published papers on
21 anthralin versus anthralin plus steroid. They clear a
22 little more quickly with the combination, but then they stay
23 clear longer without the steroid.

24 And I just wonder, while we've got both of these
25 experts here, they could comment on putting that bit of

1 information into assessment of efficacy, how long.

2 DR. LEBWOHL: Actually, Dr. Stern addressed
3 something that was key, which is how long do you stay clear
4 afterwards, and I think that is really important to
5 patients. And that combination anthralin versus anthralin
6 plus steroid, you can do great with the anthralin plus
7 steroid, but the issue is what about relapse rates. And it
8 seems that if you use monotherapy, you do better, and I
9 believe that that study showed there was--although you clear
10 more quickly--the same as been shown with UVB. Steroids and
11 UVB will let you clear a tiny bit faster, on the average
12 about a week in a three-month course of treatment, but the
13 rate of relapse is much faster. And very few patients are
14 willing to--you know, they'll be very happy to go the extra
15 week and get months more of remission without the steroid.

16 DR. STERN: I agree with Mark, and that was one of
17 the main points of my talk, that when **you** talk about four-
18 to eight-week studies, you are talking about studies that
19 encompass one-five-hundredth to one-three-hundredth of the
20 average person's lifetime of psoriasis, and making a
21 person's appearance better for that period of time is really
22 not very meaningful in the overall context of their life.
23 And one of the greatest burdens is the burden of continual
24 therapy.

25 So it really is very different to me, a therapy

1 that is remittive, even for a reasonable period of time. If
2 you can use things for a month, be off a month, I think many
3 patients find that reasonably acceptable. If you use it for
4 a month with a response and if you stop it for three days or
5 a week and it's back on its way to where it was beforehand,
6 sure, it's better than placebo, but the overall impact on
7 that individual's quality of life is unlikely to be
8 substantial, and the burden of continued therapy, be it
9 outpatient phototherapy, be it topical agents or--the only
10 thing that patients don't mind is if we had a non-toxic oral
11 agent . You know, if you had methotrexate without worries
12 about acute and long-term toxicity, we wouldn't be having
13 this meeting here today, because that is an agent--that is a
14 dosage schedule that patients find--patients who don't have
15 either the acute or chronic toxicity, in fact, find quite
16 acceptable and would be willing to treat themselves one day
17 a month indefinitely if it were not for the adverse effects.

18 CHAIRMAN MCGUIRE: Dr. Tschen?

19 DR. TSCHEN: Just a comment. My comment is: Are
20 we really increasing our expectation just with psoriasis?
21 Because we deal with a lot of conditions such as XMI (?)
22 topic dermatitis, acne, for example, which essentially we're
23 not curing completely, simply with a few medications we are
24 improving them for a long while. And we are just (?)
25 with psoriasis and expecting them to be clear forever, when

1 we are not even clear in XMI topic dermatitis, and even dry
2 skin, you know, we improve it with our own treatment, and
3 certainly are we expecting and trying to really ask that
4 psoriasis be improved for longer than any other medical
5 condition we deal with. And that's my only point.

6 CHAIRMAN MCGUIRE: I'm not sure that I got the
7 same sense of that. What I heard was that the duration of
8 remission should be one of the factors that is considered in
9 evaluating a treatment. Not that we're setting a higher
10 standard for psoriasis than we have for a topic dermatitis,
11 for instance.

12 Let's see. Dr. Drake and then Dr. DiGiovanna.
13 And then I'd like to go to the FDA presentation.

14 DR. DRAKE: Well, I think you just stated what may
15 question was going to be. I wanted to ask the experts. I
16 heard you say very clearly PASI is PASI, **and** I agree with
17 you, but do you think that in clinical trials remission--
18 most of those clinical studies are just does it clear and
19 you're done. And most of the clinical studies don't have
20 time to remission built in, although some of the more
21 progressive studies do now. Should that be a requirement,
22 in your opinion, that there be a time to remission with all
23 the studies?

24 DR. STERN: Yes. If the purpose of a package
25 insert is to describe the indications and effectiveness of

1 the drug in a way that a patient or a prescriber can make a
2 judgment about, a robust judgment about efficacy for an
3 indication, I think it should be required.

4 DR. DRAKE: Mark?

5 DR. LEBWOHL: Well, I'll tell you that it depends
6 on the individual trial, but for an average clinical trial
7 for a new drug, one of the points of differentiation between
8 vehicles certainly ought to be duration of time to
9 remission, sure.

10 CHAIRMAN MCGUIRE: Dr. Wilkin, a comment?

11 DR. WILKIN: Yes. Actually, we could modify the
12 questions in a way where the committee could give us advice
13 on both primary and secondary endpoints. The primary would
14 be the efficacy, successful outcome, and it might be limited
15 to the dichotomous or some other sort of scale, and then the
16 secondary endpoints are the kinds of things that can be
17 incorporated into the labeling, especially the clinical studies
18 section of the labeling, that might speak to issues such as
19 ease of application, how long remission lasts, time to
20 remission, these sorts of things. There is a place for that
21 in the labeling, but those would be secondary endpoints.

22 DR. STERN: Exactly.

23 CHAIRMAN MCGUIRE: John, you had a question?

24 DR. DiGIOVANNA: Yes, but I think Dr. Wilkin got a
25 partial jump on me. I enjoyed both presentations, and I

1 can't find very much to disagree with in any of them, except
2 that I think that there are--if we are looking--about asking
3 questions about grading scales, we really should look at
4 what we want to do with that information in the grading
5 scale. And I think that the answers to many of the
6 questions that were raised are answers that we all want to
7 know when we treat a patient for practical purposes. I
8 don't know if all of that information is something that's
9 appropriate for the FDA or the FDA is able to collect in
10 getting a company to do various types of studies. So I
11 certainly would like to know that a new, very expensive
12 therapy is going to be more effective than other therapies.
13 But I don't know exactly if that is the kind of information
14 that is going to be able to be collected.

15 I think that if we focus on exactly what kind of
16 information needs to be collected, it gets rid of a lot of
17 the muddling of the many different types of psoriasis and
18 location of the lesions and those sorts of issues.

19 So I guess what I'm asking is: How much
20 information do you really want to collect in a grading scale
21 and in doing these studies? And how much can you collect?
22 And that should sort of steer us into exactly what is
23 necessary in a grading scale.

24 If it's only efficacy, then many of the grading
25 scales that are very simple work. If it's clearing, then

1 you don't need a grading scale at all because everybody will
2 agree when the patient is clear.

3 DR. WILKIN: I think some of this will come out in
4 the FDA's presentation of the ways to think about it. If it
5 is, for example, the PASI scale, you know, there's this
6 edging up. You might have a mean score at the end of the
7 active of group and a mean score at the end of the inactive
8 vehicle-only group. And it might be statistically
9 significant, those scores, the difference.

10 Is that clinically relevant? I mean, I think that
11 is the very key question that we would like to hear today,
12 is what would be a clinically relevant endpoint that should
13 be the bar for these preparations. What should be the
14 minimum they should achieve? And it can be portrayed in the
15 clinical studies section.

16 Now, you know, if the committee would decide that.
17 clearing is important, how we would interpret that would be
18 that more subjects would clear on the medication than on the
19 vehicle. So it still wouldn't require everyone--it could
20 actually be a small number, but we could report those
21 numbers in the clinical studies section of the labeling in a
22 way that might be meaningful. It wouldn't be direct
23 comparisons, but if you can tell us something about entry
24 criteria, we might be able to, you know, design the entry
25 criteria in a way that there would be some comparability

1 across the board.

2 I have to tell you that is not, you know, the goal
3 in the Code of Federal Regulations for us to make
4 comparisons between products.

5 CHAIRMAN McGUIRE: Well, we will continue dealing
6 with those issues as we go on this morning and afternoon.

7 We'll have the presentation from the FDA with Dr.
8 Srinivasan and Dr. Hen-Sum Ko, in some order. Dr. Hen-Sum
9 Ko is first.

xx 10 DR. KO: Mr. Chairman, ladies and gentlemen, today
11 we are here to discuss clinical trial design for psoriasis.
12 Basically, today we are trying to focus on endpoints used in
13 clinical trials for psoriasis rather than into all the
14 aspects of these clinical trials.

15 My presentation will attempt to go through drug
16 development for stable plaque psoriasis, and to show you
17 some of the endpoints commonly used in the applications that
18 we receive, and then we will turn over to give you those
19 questions that you will be addressing to help us find out
20 what would be the most useful endpoints for regulatory
21 purposes.

22 Now, Dr. Stern and Dr. Lebowhl have covered quite
23 a lot of things this morning, and they overlap with some of
24 the material that I will be presenting. But maybe I will be
25 Looking at this through a different perspective, that is,

1 from the perspective of a regulatory agency.

2 Next, please.

3 As you know, the mandate of the agency is
4 regulatory, and in the Center for Drug Evaluation and
5 Research, our mission is to assure that safe and effective
6 drugs are available to the American people. To attempt to
7 achieve this mission--next slide, please--we tried to make
8 significant improvements in human health through excellence
9 and innovation in drug regulation. Excellence because good
10 regulatory decisions must depend or be based on good
11 science, and we need your scientific opinion to help us.
12 Innovation because there may be paradigm shifts if new ideas
13 provide sound basis for new policies.

14 In fact, today's discussion, even though it is or.
15 psoriasis, may have broad implications for endpoints in
16 other disease entities.

17 Next slide, please.

18 I tried to go through the 1998 PDR to see the list
19 of antipsoriatic agents. There are some pretty ancient
20 agents, like tar, hydrocortisone, methotrexate, and
21 psoralin(?). These were approved very long ago.

22 Next slide, please.

23 Over the last 20 years, in the PDR there are 24
24 drugs listed that have been approved within that span, from
25 1977 to 1997. One-third of these--that is, eight of them--

1 were approved between 1977 and 1986. Most of these were
2 corticosteroids or topical corticosteroids. And over the
3 next seven years, there were nine approvals as listed in the
4 PDR. Again, most of those were topical corticosteroids.

5 Next slide, please?

6 The 1998 PDR listed seven drugs that have been
7 approved in the last four years, which is about one-third,
8 again, of those 24 drugs. In fact, this is not all because
9 there are three others that have not even come to the PDR,
10 so it is a total of ten, and I have not listed Pendow (?)
11 cream, Locorilipo (?) cream, and Desoric (?) gels.

12 Now, within these last 20 years, the endpoints of
13 the clinical trials for psoriasis have really been fairly
14 consistent with primary emphasis on clinical signs and, to a
15 lesser extent, on area of involvement.

16 Next slide, please.

17 As the previous speakers have discussed, plaque
18 psoriasis, its hallmark really is monomorphic, with red
19 scaly plaques. And there are three cardinal clinical signs:
20 scaling, erythema, and plaque elevation. The symptoms
21 include pruritus and pain as well as sometimes bleeding and
22 others. The course can be quite variable with remission and
23 relapse. And the region of involvement can have significant
24 bearing on the disease. Again, this has been discussed by
25 previous speakers.

1 The goals in psoriasis trials include looking at
2 severity of these lesions, the extent or area of disease,
3 and in some applications, these include also disease-free
4 intervals, although this is not very commonly done.

5 Another goal in psoriasis trials is to look at
6 functional restoration for the very severe cases,
7 especially, those that have significant disability.

8 Next slide, please.

9 As you are all aware, there are several phases in
10 drug development. During the Phase II stage, the aim is to
11 find the greatest severity of psoriasis for which a product
12 is efficacious. And industry selects the brackets to study
13 through their inclusion criteria and tries to find out the
14 effect of the product, and usually it is tested against
15 vehicle to determine the drug effect so that a Phase III
16 trial can be planned using the result of the Phase II study.

17 Now, the inclusion criteria determines what
18 exactly the severity is in these studies, and to include a
19 restricted kind of population in these studies may not
20 reflect for the general population. So that in Phase III
21 trials--next slide, please--the goal is to really open up
22 and have more inclusive type of criteria so that the drug
23 can be shown to be effective over a larger population. And
24 at this stage, the drug is studied to demonstrate its
25 efficacy with meaningful clinical endpoints.

1 So today we ask what are the endpoints--really
2 what are the meaningful clinical endpoints. (?) with
3 documents from the International Conference on
4 harmonization. What I'm going to do is to quote from
5 Document E9 liberally.

6 Next slide, please.

7 The primary variable should be the variable
8 capable of providing the most clinically relevant and
9 convincing evidence directly related to the primary
10 objective of the trial. The selection of the primary
11 variable should reflect the accepted norms and standards in
12 the relevant field of research, and there should be
13 sufficient evidence that the primary variable can provide a
14 valid and reliable measure of some clinically relevant and
15 important treatment benefit in the subject population
16 described the inclusion and exclusion criteria.

17 In many cases, and especially when treatment is
18 directed at a chronic rather than at an acute process, the
19 approach to assessing subject outcome may not be
20 straightforward. Then it should really be carefully
21 defined.

22 Next slide, please.

23 As discussed by Dr. Lebowhl, the elevation of the
24 three cardinal signs is usually done clinically on an
25 ordinal scale shown, for example, on this slide, with 0

1 They are discontinuous As I said earlier, 0 is **none**, 1 is
2 mild, 2 is moderate, 3 severe, and so on. And they are
3 supposed to be mutually exclusive classes that form an
4 ordered series. This is a hierarchy or rank ordering. It
5 tells you "moreness" but not how much "moreness." Some
6 examples of these are like stages of cancer or education
7 level. And the clinical sign scoring systems for psoriasis
8 are generally in this category. And one cannot be really
9 sure of the distance between the scores.

10 Next slide, please.

11 Now, in this one, the upper picture shows you how
12 a severity scale is usually defined: none, mild, moderate,
13 and severe. But when it is actually used by an
14 investigator, there can be these ranges of not totally
15 defined, so there is variation between investigator and
16 investigator. And another thing that we might look at is
17 that a difference, for example, in this particular
18 investigator, a difference for scoring of 1 may be between
19 the very high part of mild and low part of moderate. And it
20 can also be one if it is a very low part of mild and high
21 part of moderate. I don't have a pointer here, so I will
22 just assume that you know what I'm referring to in this
23 picture.

24 Next slide, please.

25 Ideally, the scale is supposed to be linear,

1 but . . . what I was referring to earlier was that a difference
2 between here and there is given the same score as this and
3 there for a change in the severity scale.

4 Now, another kind of scale involves a sixth point
5 with the addition of minimal and very severe, but then some
6 studies use minimal as a half score and some use it as a
7 complete score. And this really can be confusing to
8 investigators.

9 Next slide.

10 Okay. Measurement of change. As I mentioned
11 earlier, the treatment effect is often measured in terms of
12 a change from baseline. In other words, the study gets the
13 patient's baseline severity, and then at the designated time
14 point, another assessment gives another score, so that these
15 two scores give you the change. In some studies, the
16 assessment is by the change expressed as a percentage of the
17 baseline scoring.

18 Now, this assumes that change is due to the
19 proposed treatment. We may have to assume that that is the
20 case if everything is controlled properly between the
21 treatment arms, and we also assume that measurement at both
22 time points are done accurately and in a consistent manner.
23 Now, as I showed in the previous slides, there may be some
24 question on that.

25 Another thing is that the scores have to be

1 subtractable. If you have scores like what I have just
2 shown you where there may be overlaps between investigators
3 and there may be differences that are not equal in between
4 the same reduction, then these subtractions may become also
5 questionable.

6 Next slide, please.

7 Again, this is about the objectivity in these
8 assessments, and I am just quoting from Edwards, that the
9 eye-brain system is not very good at linear quantitation of
10 what it sees, and both memory and experience will affect
11 judgment of lesion severity.

12 Next slide, please.

13 There are some attempts with using instrument
14 measurement of the clinical signs, but we don't really have
15 much of these in the studies that we receive, in the
16 applications. And even if we use instrument measurement,
17 there are still differences between these clinical signs in
18 terms of the actual evaluability because erythema and
19 scaling are subject to rapid fluctuation in intensity after
20 relatively minor stimuli, and only partially reflect the
21 severity of psoriasis; whereas, plaque thickness may be a
22 more reliable indicator of the disease progress as this
23 parameter reflects epidermal thickness, edema, and cellular
24 infiltrate.

25 This leads me to the next slide about the total

1 scoring. As I said, in many applications a total score is
2 given by adding up the clinical signs, and **sometimes** also
3 including pruritus **And since in the last slide you saw**
4 that there is some **difference between these three** clinical
5 signs in terms of their evaluability, really it is difficult
6 to be just using a total score without some qualification or
7 weighting process.

8 Other issues are that the total score is a
9 dependent variable, subject to all the pitfalls of the
10 components. And just like we may have an issue of
11 subtracting the scores, now adding the scores also may
12 introduce a problem. Again, I have asked the question
13 **earlier** about whether they should be weighted.

14 Next slide, please.

15 I think both speakers previous to my presentation
16 have gone through PASI with you, and I think I will just not
17 spend a lot of time on this one. As Dr. Stern pointed out,
18 it may be really at odds with **what** is clinically important.

19 Another issue I have with this is that you are
20 really using a weighted scale by multiplying area with
21 severity, and the multiplication may magnify these possible
22 **errors**, particularly because, as you know, evaluation of
23 **area** is not very accurate, at best.

24 Next slide, please.

25 In quite a lot of applications over the last ten

1 years, sponsors have been using so-called target lesions for
2 the evaluation. In other words, they select certain typical
3 lesions with some minimal criteria and give the severity
4 scoring and also an overall assessment of each lesion. This
5 is because there may be heterogeneity of these lesions in
6 psoriasis, and frequently a distinction is made between
7 those over the trunk, arm, or legs, versus those over bony
8 prominences, which are presumably more difficult to treat.

9 Next slide, please.

10 Now , I am quoting again from the E9 document of
11 ICH. When the clinical effect defined by the primary
12 objective is to be measured in more than one way, the
13 protocol should identify one of the measurements as the
14 primary variable on the basis of clinical relevance,
15 importance, objectivity, and/or other relevant
16 characteristics whenever such selection is feasible.

17 Another strategy that may be useful in some
18 situations is to integrate or combine the multiple
19 measurements into a single or composite variable using a
20 predefined algorithm. This approach addresses the
21 multiplicity problem without requiring adjustment for
22 multiple comparisons. And the method of combining the
23 multiple measurements should be specified in the protocol
24 with an interpretation of the resulting scale should be
25 provided in terms of the size of a clinically relevant

1 benefit.

2 When composite variables are used as primary
3 variables, the individual components of these variables are
4 often analyzed separately, and total scores may be
5 considered as one of these if it is used as a primary.

6 Next slide, please.

7 Again, I am quoting from the E9 document. In some
8 cases, global assessment variables are developed, and this
9 type of variable integrates objective variables and the
10 investigator's overall impression about the state or change
11 in the state of the subject, and it is usually a scale of
12 ordered categorical ratings.

13 Now, please note that there are two ways of doing
14 this. One is using the state and the other is the change in
15 the state. I will have more to say about this in the next
16 slide, but here, the same slide, on these global assessment
17 variables, they generally have a subjective component. And
18 so fuller details should be included in the protocol with
19 respect to the relevance of this global scale to the primary
20 objective of the trial, the basis for the validity of the
21 scale, and how to utilize the data collected on an
22 individual subject to assign him or her to a unique category
23 of the global assessment scale.

24 Now, we will be going over these again later.

25 If objective variables are considered by the

1 investigator when making a global assessment, then those
2 objective variables should be considered additional primary
3 or at least important secondary variables. So if we are
4 going to use a global as a primary, then maybe we will take
5 the individual clinical signs or total scoring as an
6 important secondary, if not another primary.

7 Next slide, please.

8 As I said earlier, there are two kinds of global
9 assessment . One is the static global, assessing the overall
10 picture of the condition or lesion, that is, the state.
11 Another one is using improvement from baseline, or change of
12 state. And the next slide will give you an example of
13 improvement .

14 Next slide, please.

15 Improvement from baseline. You can see that
16 frequently these scales are given in terms of percentage
17 change from baseline, and this may be done for the whole
18 patient or for a single lesion. These are ordinal scores
19 without need to have uniform distance in between. As you
20 can see, one of the scores may be between 1 to 49 percent,
21 whereas one is between 90 to 99 percent. These are
22 subjective estimates of percentage, again, with inter- and
23 intra-investigator variability.

24 One big drawback about this kind of scoring for
25 global is that it is memory-dependent, and that may

1 introduce bias. It may or may not take the size of involved
2 area into account in considering the improvement.

3 Next slide, please.

4 So as you remember, the last slide showed that
5 these improvement globals require memory. Now, in Streiner
6 and Norman's book, "Health Measurement Scales," there is
7 this statement: It seems that the most defensible way to
8 assess change for estimating individual growth or treatment
9 effects is really to directly measure the attribute at the
10 beginning of study and subsequently on one or more
11 occasions.

12 Next slide, please.

13 This brings me to the other kind of global or
14 static global, and some studies may call that overall
15 lesional severity. It is static, non-moving. We're looking
16 at one particular time point, and it is not relating to a
17 change from baseline. It's global as it expresses the
18 overall lesional severity, again, either a local lesion or
19 maybe the overall picture of the patient.

20 One example used in an application is shown here,
21 showing that the score of 0, or cleared, requires that the
22 patient has no more scaling or plaque elevation, but
23 allowing some dusky red erythema; and 1 being minimal, it
24 has some plaque elevation, but still no scaling. And
25 erythema is allowed up to moderate.

1 Now , I am only giving you an example of one of
2 these that we get from time to time, and they may be
3 different from study to study, depending on the sponsor.

4 This kind of scale is memory-independent, and it
5 incorporates information from the cardinal signs together.

6 Next slide, please.

7 Now, here I am comparing the two types of global
8 according to the ICH E9 document. The first one, the
9 relevance of the global scale to the primary objective of
10 the trial. I presume from the previous speakers that most
11 of us do want clearing as an objective of the trial. So the
12 question is: If we use the improvement from baseline type
13 of assessment, are we assessing edging up or are we also
14 aiming only at the clearing layer of that scale? Whereas,
15 if we are looking at the static global, then we are looking
16 at distinct features of different gradations of the severity
17 with hopefully clearing as our objective.

18 Second, the basis of the validity of the scale.
19 Again, I mentioned earlier that one big drawback of the
20 improvement type of global depends on memory, while the
21 static global does not.

22 Third, how to utilize the data collected on an
23 individual subject to assign him or her to a unique category
24 of the global assessment scale. With the static global, we
25 can really integrate the clinical signs fully into the

1 picture; whereas, with the improvement from baseline type of
2 global, this is more difficult.

3 Next slide, please.

4 One of the questions you will be addressing today
5 is about dichotomization, and so I am going to say a couple
6 of words, and Dr. Srinivasan will be going through this in
7 more detail with you.

8 Essentially, we're looking at a responder
9 analysis, success or failure. Now, why do we want to
10 dichotomize? Again, I'm quoting liberally from the E9
11 document.

12 Dichotomization or other categorization of
13 continuous ordinal variables may sometimes be desirable.
14 The criteria of success, as with end response, are common
15 examples of dichotomies that should be specified precisely.

16 Categorizations are most useful when they have
17 clear clinical relevance. The criteria for categorization
18 should be predefined and specified in the protocol as
19 knowledge of trial results to easily bias the choice of such
20 criteria.

21 Next slide, please.

22 Now, why do we want to dichotomize? This leads
23 back again to what we have been discussing this morning as
24 what is the most clinically relevant thing, and clearance is
25 unambiguous and clinically most relevant.

1 For non-infectious disorders, it may be acceptable
2 to have a nearly cleared category as a successful outcome as
3 well .

4 Now , these types of outcomes help to develop
5 products that provide meaningful benefit, not just edging
6 up, and such data are also more informative in the labeling
7 rather than simply giving mean or median score.

8 Now I will turn over the podium to Dr. Srinivasan
9 to discuss more about dichotomization.

10 CHAIRMAN MCGUIRE: Thank you very much. Not so
11 fast.

12 Let's see. It's 10:47. I think that what I would
13 like to do, unless I hear to the contrary, is take a break
14 at this point, and pick up again at 11:15 and start promptly
15 at 11:15 for the remainder of the FDA presentation. Is that
16 acceptable?

17 [Recess.]

18 CHAIRMAN MCGUIRE: Can the Advisory Committee come
19 to the table, please?

20 Dr. Srinivasan will continue the FDA presentation..

21 DR. SRINIVASAN: Thank you, Chairman, other
22 committee members. Thank you, Hen-Sum, for letting me
23 present statistical aspects related to the endpoints of
24 stable plaque psoriasis.

25 In the beginning of Dr. Hen-Sum Ko's presentation,

1 he showed a few slides where he traced the history of drugs
2 for psoriasis approved by the agency. In approving those
3 drugs, the agency has looked at the primary efficacy
4 endpoint, global evaluation.

5 If the global evaluation has a categorical scale
6 and all-category comparison is used, then we can observe a
7 phenomenon called edging up.

8 First slide, please.

9 This is an example of the static global scale
10 ranging from 0, which is clear, to 5, which is severe. 0 is
11 no scaling, no elevation, no erythema; 1, the absence of the
12 first two and a dusky erythema; 2, 3, 4, and 5 are defined
13 accordingly.

14 Due to randomization, at baseline the distri-
15 butions of global evaluation scores in the two treatment
16 groups are usually aligned. Suppose we observe edging up,
17 which means patients from grade 5 to move to grade 4 or from
18 grade 4 to move to grade 3. Suppose that more patients in
19 the active group show edging up than in the placebo group.
20 Then at the end of the treatment, we will observe a shift
21 between the distributions in the treatment groups.

22 If the sample size is large enough, a
23 statistically significant difference between the treatment
24 groups will be observed. This statistical superiority of
25 the active arm over placebo may not be meaningful for the

1 doctor and the patient because they are not satisfied just
2 by the fact that at the end of the treatment there is a
3 statistically significant difference in status quo
4 distribution between the treatment groups. What doctor and
5 patient want to see in the label is that at the end of the
6 treatment significantly larger proportion of patients in the
7 active group had clear skin. For this reason, we recommend
8 dichotomization of global evaluation.

9 Next slide, please.

10 For example, we recommend success in the global
11 evaluation as clear or almost clear at the end of the
12 treatment. This is just an example.

13 Can you **put on the third slide, please?** I will
14 come back **to the second.**

15 For example, in the global evaluation scale shown
16 in this slide, success will mean 0 or 1, and failure will
17 mean grades 2 through 5. This is just an example, and we
18 would like the committee members to help us with other
19 possible alternative methods of dichotomization. Success
20 rate in global evaluation by investigators is being
21 recommended as a primary efficacy variable.

22 Next slide, please.

23 Success rate in the active treatment group
24 relative to global evaluation does not have to be very high.
25 For example, there may be a 20 percent success rate in the

1 treatment arm and 4 percent success rate in the placebo arm,
2 so that is the reason I said that it does not have to be
3 very high. So approval is only contingent on the test drug
4 being statistically superior to placebo.

5 In the label, it is more meaningful to present the
6 results of clinical trials in terms of success rates. For
7 example, X percent of subjects in the treatment group were
8 clear or almost clear at the end of treatment compared with
9 Y percent in the placebo group.

10 Next slide, please.

11 Let me talk briefly about the statistical methods.
12 Comparison of success rates between active and placebo
13 groups should be performed using Cochran-Mantel-Haentzel
14 procedure adjusting for investigator. I would like to
15 caution a little bit in this in the sense that if the
16 expected cell frequencies are less than five, probably
17 Cochran-Mantel-Haentzel test may not be the appropriate
18 procedure. In such a situation, we would like to seek exact.
19 test procedures, and built-in in the Cochran-Mantel-Haentzel
20 procedure is a test called Breslow-Day test, which will show
21 whether the observed relationship between treatment and
22 success is homogeneous across investigators.

23 The division does not recommend the use of Chi
24 square or Fisher's exact test because these tests do not
25 adjust for investigator.

1 1 will now pass the podium back to Dr. Ko for
2 continuation and wrap-up. Thank you.

3 DR. HO: Thank you, Dr. Srinivasan.

4 I am continuing our discussion on dichotomization
5 of global. Although to use this as a primary efficacy
6 variable may appear to be new in a certain sense, it is not
7 entirely new. We have usually looked at both global and
8 clinical signs together.

9 For dichotomization of the global in terms of
10 success and failure, it has also been used in the approval
11 of other drugs such as the recent approval of TPA in stroke.
12 And so these are not exactly new ways of looking at the
13 success of the drug.

14 Now, let me turn back to the discussion on where
15 we should have the cutoff for success. Dr. Srinivasan has
16 discussed with you how the cutoff can be made between the
17 different grades and the statistical methods of analyzing
18 them. And, really, today's meeting, we would like you to
19 give us input on where the bar should be placed.

20 Ideally, we would like the patients to have
21 clearing, and possibly nearly cleared, since this is really
22 not an infectious diseases. But maybe there are also some
23 acceptable levels that we can be comfortable with, and we
24 would require your input on that.

25 Next slide, please.

1 This is just to show you again a slide that you
2 have seen earlier about why we want cleared and nearly
3 cleared. The eye-brain system is not very good at linear
4 quantitation of what it sees, and both memory and experience
5 will affect judgments of lesion severity. So if we use the
6 comparison with baseline kind of global, which involves
7 memory, this will present difficulty with memory and
8 experience causing bias. Again, our question to you is to
9 tell us what else may be acceptable.

10 Next slide, please.

11 I am not going to go through quality-of-life
12 evaluation because, first, we have had discussion earlier by
13 two previous speakers, and we do not get many applications
14 that include this kind of parameter in the studies.
15 Occasionally we get some that include them, but they are not.
16 used as primary or even secondary variables. They just
17 present the data.

18 Next slide, please.

19 Just to end the discussion on quality of life, I
20 want to quote Dr. Armstrong, who said that severe adverse
21 reactions that are accompanied by clinical improvement may
22 result in a net improvement in the quality of life as judged
23 by one patient and the opposite conclusion may be reached by
24 another patient. And that is one of the problems.

25 Next slide, please.

1 so, to summarize, I would like to list the
2 questions that you have in front of you.

3 Regarding the entry criteria, should the clinical
4 trials for plaque psoriasis include some minimal criteria
5 for severity of the clinical signs and some minimal surface
6 area of involvement?

7 Regarding the endpoints, we have a question on the
8 dichotomous outcome. We would like for you to discuss
9 whether a dichotomous outcome for the global evaluation be
10 preferable to an all-category comparison as the primary
11 endpoint. And if you do think so, then where should we
12 place the bar for this dichotomous outcome?

13 Regarding the cardinal signs--plaque evaluation,
14 scaling, and erythema--should they carry equal weights or
15 carry different weights? And how should these scores be
16 combined as another endpoint?

17 Next slide, please.

18 We have not really addressed area of involvement .
19 We would like you to discuss whether area of involvement be
20 included in the analysis of outcomes. And if so, how?

21 Regarding the heterogeneity of lesions, should
22 there be stratification for certain lesions, for example,
23 those over the bony prominences?

24 And, finally, to what extent can quality-of-life
25 assessment be used in the evaluation of success in the

1 treatment of psoriasis?

2 Thank you very much.

xx

3 CHAIRMAN McGUIRE: Thank you.

4 Are there questions that we can direct toward the
5 two speakers from the agency? Yes, Dr. Kilpatrick?

6 DR. KILPATRICK: I'm not really addressing this
7 necessarily only to the two speakers from FDA, but maybe
8 also to other members of the committee in addressing these
9 points.

10 It seems to me that some of these questions need
11 to be phrased in the context of whether we are talking about
12 topical or systemic treatments, because it seems to me that.
13 a topical treatment, the patient can be used as his own
14 control; whereas, in two-arm studies, as Dr. Srinivasan
15 mentioned, we might have the conventional two-arm study with
16 different patients assigned randomly to each of those. One
17 of these is quite explicit. Should area be being
18 considered? That would be obvious in the first of these but
19 not necessarily in the second. But I would like just to
20 make that point before we start discussing the answers to
21 these questions.

22 CHAIRMAN McGUIRE: Jon, if I could make a brief--
23 well, go ahead with your remark, and then I'd like to say
24 something.

--
25 DR. WILKIN: Okay. Well, I think Dr. Kilpatrick

1 has raised an important issue that is not really clarified
2 in the phrasing of the questions. In Phase III, we don't
3 really like to see paired comparisons, that is, one side of
4 the body versus the other side or one lesion on the one arm
5 versus a lesion on the other arm, because emerging from the
6 Phase III pivotal trials, we want information not only about
7 efficacy but also about safety. So we'd like to see all of
8 the lesions in that particular patient being treated. We
9 think that gives us the best. So there are parallel designs
10 for both topical and systemic.

11 Perhaps one of the other distinctions between
12 topical and systemic, one might think that topical is by its
13 very nature more safe and systemic less safe, and I would
14 urge the committee not to adopt that view because topical
15 medications can be readily absorbed and systemic medications
16 may have a fairly benign side-effect profile.

17 So we're really talking about the usual kinds of
18 psoriasis medications. If there's something unique about
19 the safety profile, those are the kinds of issues we bring
20 to the committee, and often the way the committee has
21 suggested in the past of working with those is restricting
22 the entry criteria, the kinds of patients that would be
23 eligible. It might be recalcitrant disease, might be some
24 other factor.

25 CHAIRMAN MCGUIRE: I would like to make a few

1 comments that will--these are all truisms so you don't
2 really have to listen carefully.

3 [Laughter.]

4 CHAIRMAN MCGUIRE: But we're dealing with a
5 disease of management. We're not dealing with
6 meningococccemia. We're dealing with a chronic disorder.
7 And it's a delusion on our part to think that we're looking
8 for a cure. We're looking for durability of remission.

9 The criteria that have been listed as indicators
10 for severity of disease are quite treacherous. Many of you
11 remember in the 1970s and 1980s when we would admit patients
12 with extensive psoriasis to the hospital and the extensive
13 scale that had been present for the last year disappeared
14 overnight. That was easy. And the next day the patient
15 said, What's going on here, I'm bright red.

16 Well, they were red to begin with, but you
17 couldn't see it because they were covered with scales. So
18 there's this reciprocity of scale and erythema that can be
19 quite misleading. So I don't know how we're going to factor
20 that in, but at least in the initial clearing phases, we
21 have to be careful that we're not unveiling erythema by
22 removing scale.

23 It seems to me that the two most reliable markers
24 for severity of disease are area of involvement and
25 thickness of lesion, and I would put those two--if I had to

1 take my choices, I would pick those two measurements as more
2 valid indicators of the severity of the disease.

3 Now , the good thing about being Chairman, I can
4 just say that and that gives you an opportunity to tell me
5 the way it really is. And I would open it up to all the
6 panel now. Dr. DiGiovanna?

7 DR. DiGIOVANNA: I have no intention of telling
8 you the way it really is. I do have a question with respect
9 to what would be the outcome of our suggestions to the FDA.
10 Whether or not if we suggest that psoriasis studied should
11 be done with a grading scale of a certain type, does that
12 mean that that will be a requirement for all comers such
13 that if someone wants to study psoriasis in a different way,
14 they will have an impediment to doing that? In other words,
15 will we be establishing a standard to which others will be
16 held?

17 DR. WEINTRAUB: Okay. Let me first tell you that.
18 this is an advisory committee, and we take your advice very
19 seriously, but we don't have to follow it if we disagree.

20 [Laughter.]

21 DR. DiGIOVANNA: I understand that. That wasn't
22 what I was asking.

23 DR. WEINTRAUB: Right. Okay.

24 CHAIRMAN McGUIRE: You know, he has said this
25 before.

1 DR. WE INTRAUB: I say it every meeting once. I
2 had to get it in this time, too.

3 However, so what we are looking for is your
4 feeling about what are the important points that we should
5 be taking into account in asking sponsors to study
6 psoriasis. That's what we're really looking for.

7 So I wrote a note to Jon before. I said--and
8 basically to Karen as well, to Dr. Weiss, that we should be
9 writing the results of this meeting and our own thinking up
10 as soon as we get back, as soon as we can, just a few miles
11 down 270, because it will give us an opportunity to think
12 about these things and write them down to communicate with
13 the industry.

14 DR. DiGIOVANNA: So we're not establishing
15 necessarily--or you are not necessarily going to establish a
16 standard from this, is what you're telling me.

17 DR. WEINTRAUB: Well, I don't know. We hope to
18 establish a standard.

19 DR. DiGIOVANNA: I guess what I'm really trying to
20 say is that from my perspective--and certainly based upon
21 what we've heard from the two excellent presentations this
22 morning--psoriasis is an extraordinarily variable disease.
23 In addition, the treatments are of a very wide range
24 compared to many other treatments. I mean, we have, you
25 know, light treatments, we have systemic drugs, and we have

1 topical treatments and all sorts of things, plus a whole
2 variety of other issues that weren't raised. Some of those
3 treatments may require particular ways of evaluation that
4 are not necessarily appropriate for other treatments, one of
5 which has been suggested is certainly that, I think,
6 systemic or total body treatments are more appropriately
7 evaluated in a different way than topical treatments which
8 can be evaluated just locally.

9 But , in addition, there are certain, let's say,
10 topicals that may have certain characteristics. A topical
11 retinoid may cause redness during the process of treatment,
12 and that may confound your measurement of redness. And
13 there may be issues that are specifically related to a
14 modality. Certainly the erythema that, you know, light
15 causes the--so I guess what I'm saying, there probably needs
16 to be some kind of a sense that we--my concern was in saying
17 this is the way psoriasis should be evaluated and having
18 that become a standard, when someone develops a treatment in
19 the future that may be--you know.

20 DR. WEINTRAUB: Right, innovative. We're also
21 willing to include different treatments and especially
22 innovative treatments that have to be looked at in
23 innovative fashions. We're entirely willing to do that, and
24 I urge--we frequently see people who come in very early in
25 the course of development of medication. Before they even

1 file an IND, we'll talk to them and see what studies can be
2 used to evaluate that treatment.

3 But, by and large, we are hoping to arrive at
4 something that we can discuss, put out to industry, have
5 their comments, put out to the committee, have your
6 comments, and work together to establish a standard for run-
7 of-the-mill psoriasis therapy. Because, I mean, we feel
8 that establishing those endpoints would be very valuable,
9 and this is the time to do it.

10 I think we're on the threshold of--I hope we're on
11 the threshold of a whole new series of compounds, and they
12 won't be just what Hen-Sum showed you as steroids, more
13 steroids.

14 CHAIRMAN MCGUIRE: We'll hear from Dr. Stern and
15 then Dr. Weiss.

16 DR. STERN: My own belief is that what makes a lot
17 of sense would be a trichotomous evaluation, and with the
18 primary first endpoint, one of the two acceptable endpoints
19 being normalization of skin as described in the slide, with
20 one important addition that may be hard to quantify but, in
21 fact, is photographable. With many treatments, you have not
22 visible plaque in terms of erythema. You have complete
23 flattening. But, in fact, you do not have restoration of
24 normal skin markings. And if we are not going to get into
25 the whole business of duration of remission, in fact, the

1 biggest surrogate predictor for me in my experience is if
2 you don't have normalization of skin markings, you're likely
3 to have rapid return of disease, because that's not really
4 normal skin. If you biopsy it, it is not normal skin in a
5 histologic sense.

6 So I think as a primary endpoint, what you're
7 really trying to achieve is it's flat, it's not pink, and it
8 looks in terms of skin markings like the skin adjacent to
9 where the plaques used to be.

10 I think the second is basically making skin flat
11 and minimally pink and non-scaly, and I think for many
12 people, depending on the use characteristics of the agent
13 and the severity of disease, that is really real clinical
14 benefit for those individuals.

15 So on where you are trying to get, to me those are
16 the two reasonable endpoints. I think you have to realize
17 that the one complication is you can't expect any agent to
18 do it to all of the patches, so you may also need to put in-
19 -and this becomes a measurement problem--some criteria of
20 the original psoriasis, as long as X percentage reached,
21 either primary endpoint one or second endpoint, that's
22 sufficient for being successful according to those
23 endpoints. I don't think you can require an agent
24 reasonably to say, all right, all the patches have gotten to
25 be where there's normal skin markings, macular erythema, or

1 the second endpoint I have talked about. So there you get
2 into the problem of do you just use index plaques if it's a
3 topical--if it's any kind of therapy, and accept those,
4 which is one strategy; or do you--as long as you know that
5 you can't have adverse selection as to the index plaques, or
6 do you say we're going to look at all the plaques and we're
7 going to measure them in some way and be able to prove that
8 a certain proportion of them reached either endpoint one or
9 endpoint two.

10 CHAIRMAN McGUIRE: Rob, tell me how you feel about
11 using durability of remission in a chronic disorder? Do you
12 think that is something--

13 DR. STERN: I think it's wonderful. What I want
14 to know about every agent is how many people have flared
15 within--again, it depends on the kind of agent because there
16 are ways of getting around it. You can give a retinoid
17 with a half-life of weeks so the time to flare is going to
18 be longer, not because you've stopped the drug but, you
19 know, it's still there and working as it decays. So is it
20 fair to compare an oral drug with a half-life of 120 days
21 with a drug with a half-life of 8 hours? It's certainly not
22 fair unless you have convinced me that there's no toxicity
23 to that tale of drug storage. So it's very--it's
24 complicated, and I think when I evaluate a product, I want
25 to see what's the rate at 30 days and what's the rate at 3

1 to 6 months.

2 I think if I were approving a drug, it puts up SO
3 many more barriers. You know, those are very complicated,
4 expensive studies, and I'm not sure I feel it's fair. I
5 feel that that may be raising the bar if you said as a
6 clinician making decisions about using an agent, especially
7 if it might have some substantial risk or some substantial
8 cost, it's absolutely vital information.

9 CHAIRMAN MCGUIRE: My question had a little
10 different point in that if you were looking at a new
11 insulin, you wouldn't withdraw the insulin and wait for
12 ketosis. And so is it reasonable, in a chronic disorder
13 like psoriasis, to discontinue the medicine and wait for the
14 disease to emerge.

15 DR. ROSENBERG: Absolutely. People go into
16 remission, and some treatments are more likely to induce
17 remission than others. Absolutely, positively.

18 DR. STERN: And, in addition to that, in terms of
19 an agent being clinically acceptable, you have to tell me
20 how often you have to use it. So if you say you have a
21 topical--either a risk-free oral agent that you use once a
22 week or a topical agent that you only need to apply once or
23 twice a week, which has a very good risk profile, that's
24 reasonable to use it indefinitely, and every once in a while
25 you try stopping it to make sure you're not in remission.

1 But those are not the usual use characteristics of these
2 agents. If we had agents like this, we probably wouldn't be
3 having this meeting right now.

4 I'll just make one more point. I think when you
5 have these endpoints, you also have to think about not
6 thinking of all stable plaque psoriasis as the same. For
7 example, for moderate disease, which usually means less
8 area--for less area of involvement, agents that get you to
9 the less stringent of the two endpoints that are used with
10 only modest frequency for many people with moderate areas
11 covered are quite usable, quite clinically acceptable;
12 whereas, for people with severe disease, even if in a
13 clinical trial you can safely get them to that level of
14 disease, it's just not practical if they never normalize
15 their disease. And in a sense, it's a bit tied up to a
16 question you just asked me.

17 So I think you may want to think about also having
18 some division of who the agent is for, at least who your
19 protocol is addressed to. You know, I don't know exactly
20 the right words, but this is an agent that has been shown to
21 get to this point for patients who had these entry
22 characteristics, and really going a little bit more for
23 specifically defining how broad the indication is going to
24 be within plaque-type psoriasis in terms of extent of
25 disease, I guess.

1 CHAIRMAN MCGUIRE: Dr. Weiss, you had a question a
2 long time ago.

3 DR. WEISS: Yes. Well, actually, what I was going
4 to say earlier is sort of probably moot now, but I think
5 what Dr. Stern and some of the other discussion raises lots
6 and lots of different questions. I was going to actually
7 ask a little bit already about the generalizability of a
8 claim that can be made based on the patients that were
9 included in the Phase III trials, and how broadly one can
10 extrapolate from data in a particular patient population to
11 other populations is a little bit hard in the absence of a
12 real trial and real data to know.

13 Usually, questions come up in a committee
14 discussion about a marketing application about the
15 indication and how narrow to base the indication, and I
16 guess I just wanted to throw that point out because that
17 also impacts on another, I guess, question I was going to
18 bring up with respect to extrapolation of what you see in
19 the trial. In particular, the agency is moving now, as part
20 of FDA reform, towards more emphasis on pediatric patients
21 and including pediatric patients or being able to
22 extrapolate data from adults to get appropriate labeling in
23 pediatric patients.

24 The question I think I wanted to ask to this
25 committee with respect to pediatric patients with psoriasis

1 is how analogous pediatric disease is to the adult. Many
2 adults start out as having the disease as children. Is the
3 prognosis different? Is the outcome different? Would you
4 be able to extrapolate if you had a trial primarily in
5 adults because it's much more common? Can you extend some
6 of that information down to pediatrics? Or would one want
7 to see separate efficacy trials? And here I'm probably
8 talking more about probably topical therapies, understanding
9 that probably some of the systemic therapies might have a
10 lot more concerns about toxicity and you may want to wait
11 quite a bit longer before even thinking about studies in
12 children.

13 CHAIRMAN McGUIRE: Karen, you will probably get
14 ten answers to that question, and so the first answer will
15 come from Mark, who has been waiting to ask a question.

16 DR. LEBWOHL: Well, that wasn't the reason I had
17 my hand up, but my first answer is: Even in topical
18 treatments, there will be different side-effect profiles in
19 kids than in adults. For example, the tendency to develop
20 striae occurs in a really fairly--"narrow" may not be the
21 right way of phrasing it, but infants seldom develop stretch
22 marks, for example, because their skin is more elastic. Old
23 people have very tightly cross-linked collagens so they
24 don't develop stretch marks. And people in an age group of
25 about 8 to 40 develop stretch marks. And so kids are right

1 in there, and your 50- and 60-year-olds, you can't
2 extrapolate the side effects from them down to kids.

3 The same holds true for absorption of medications.
4 There are several Vitamin D analogs available around the
5 world. If we're concerned about hypercalcemia, you know,
6 you're going to be more concerned in children, possibly,
7 than you would be in adults. So you can't directly
8 extrapolate from adults to children even with a topical
9 medication.

10 But what I wanted to say was to get back to what
11 you said regarding plaque thickness as being a parameter
12 that is the least affected by extraneous issues such as how
13 humid it is that day or how much moisturizer the patient
14 applied that day or how hard they washed their skin that
15 day.

16 I am a little concerned if we make complete
17 clearing as our endpoint. Not to say that that is not a
18 good endpoint. It is a very good endpoint. But some of the
19 agents currently available that have done a lot for our
20 patients might not have even been considered if we looked at
21 that endpoint.

22 Speaking of the many Vitamin D analogs available
23 around the world, if you look at the results of any of their
24 published trials, the proportion of patients that clear
25 completely is extremely small. The same holds true with the

1 topical retinoids.

2 I was glad to hear Dr. Stern offer a trichotomous
3 evaluation because what do you call that patient who has
4 flattened their plaque completely but has residual erythema.
5 And for the patient, that may be a very good outcome, but
6 for our evaluation, if we make complete clearing, that is
7 not complete clearing. And some investigators might not
8 even all that almost clear.

9 So you're talking about proportions of patients
10 that will be likely under 20 percent, and the numbers of
11 study subjects required to obtain statistical significance
12 will be enormous. And I'm just concerned that we will
13 dissuade the development of very good drugs if we make our
14 criteria too difficult.

15 Now , it is fine if we have dichotomous criteria,
16 but that's not the only criterion for approval. So I would
17 just be careful about that. And normalization of the plaque
18 is a very good way to evaluate psoriasis. Complete
19 elimination of the plaque may be difficult, but it's easier
20 than complete clearing. And I think that it is very
21 reproducible because you can feel that with your finger.

22 CHAIRMAN McGUIRE: That's a very important point.
23 I think all of us in clinical practice--I assume that
24 everybody uses his hands to explain things to patients, and
25 you say with this Vitamin D--this is where you are and this

1 is perfect and this is where I'm going to take you with this
2 product, and then we'll have to do something else to get you
3 from here to here. And so the recognition is there up front
4 that we don't expect to get from here to here with that
5 product.

6 DR. ROSENBERG: I want to make a couple of
7 comments on this morning. First, I really welcome the
8 agency's initiative in moving towards this dichotomous, all
9 clear or nearly clear. I think this is very important
10 information for the label, for the profession, for the
11 patient. As the drugs get newer and stronger, I think the
12 regulatory response also can demand more. I don't think,
13 however, as has been said, that the bar to getting a product
14 approved, particularly a topical, should be at that level.

15 I think the approval could certainly well be, as
16 it has always been--the agency knows how to do it--as
17 compared with placebo. But I think getting information
18 about clear or all clear certainly can be demanded and
19 required and asked of applicants. I would say in terms of
20 all clear or almost clear, I'd agree with Dr. Stern that not
21 every last spot and mark necessarily has to be gone. If 85
22 spots are gone and there's one little one that just won't
23 quite go away, I think that is all right.

24 I would just--a minor quibble. The way we treat
25 psoriasis patients with antibiotic, the redness is not the

1 last thing to go. The scale is the last thing to go. The
2 redness goes first, and there's a little scale at the very
3 end. So it looks a little different, but a lot of them get
4 cleared.

5 With Dr. Stern here, we just have to say something
6 about Phase IV aspects of this, or if not Phase IV,
7 prolonged follow-up. Everybody here is grateful for the
8 pool of study and everything about it, and no less I think
9 should be required in a way, or somewhat less, perhaps, but
10 of new agents.

11 First, I think the durability of remission, as
12 everybody has said, is what patients really want. You know,
13 they ask you, Should I go to the Dead Sea? The first
14 question, they say, You get clear. I said, Yes, you get
15 clear. They say, How long do you stay clear? I say about
16 six months. And that's the second question they ask is how
17 long you stay clear from the Dead Sea. That's how long you
18 used to stay clear if you went to Mayo's for the
19 Geckerman(?). Three weeks in and six months off was about
20 the standard.

21 So these are very real things, and the safety has
22 to be done for a long time. I mean, with agents that affect
23 immune response system, I have said to people and tell
24 patients, when I started in dermatology, we were just over
25 the era of treating psoriasis with Fowler's solution and

1 organic arsenic. And the older clinicians said that it's
2 really an excellent treatment, Fowler's solution, it makes
3 the psoriasis go away, and it stays away for a very long.
4 There was only one problem with Fowler's solution, and that
5 was 25 years later the patients, some of them, got cancer.
6 And so it was taught that if either the patient or the
7 physician were over the age of 65, it was not a bad
8 treatment for psoriasis.

9 [Laughter.]

10 DR. ROSENBERG: I think we have to think that way,
11 and I think there should be a special category of assessment
12 for something that is almost as good as skin cap that can
13 get some special rating.

14 Thank you.

15 CHAIRMAN MCGUIRE: Well, I'm glad you didn't say
16 anything inflammatory this time, Bill.

17 [Laughter.]

18 CHAIRMAN MCGUIRE: Let's see. Who's next? Eva,
19 are you next?

20 DR. SIMMONS-O'BRIEN: Dr. Stern, how would an
21 investigator actually--how would normalization be defined?
22 Are you talking about clinical as well as histologic
23 confirmation?

24 DR. STERN: I would avoid histologic. I'm talking
25 about clinical, and I'm a firm believer in photography. I

1 think that having--although I don't think a treatment should
2 be judged by index plaques alone and I trust investigators
3 to tell me how much index plaques are typical or not typical
4 of what's going on, one can very easily take good
5 photographs that can be reviewed and determined whether
6 they, in fact, represent normalization of skin. So I think
7 you don't have to do anything invasive, anything more
8 invasive than a flash camera.

9 DR. SIMMONS-O'BRIEN: Because I'm just thinking
10 about some of those patients who retain permanently post-
11 inflammatory hyperpigmentation, but the lesion is gone.

12 DR. STERN: And that's something else I think you
13 can assess photographically, and I think patients--that is,
14 unfortunately for people who are predisposed in that way,
15 that is--you can't expect any agent not to do that, and I
16 think people who have normal skin markings and
17 hyperpigmentation, that's still a very good outcome for
18 those individuals. You obviously have to tell them that
19 when your psoriasis is clear, you may have hyperpigmentation
20 there.

21 CHAIRMAN MCGUIRE: Dr. Kilpatrick?

22 DR. KILPATRICK: Thank you, sir.

23 I've got two reactions to the conversations and
24 the presentations today. One, I'd like to come back to Dr.
25 Stern and revisit the suggestion that both the patient and

1 the physician may want to give a global assessment of the
2 condition after treatment.

3 In your experience, sir, how coherent were those
4 evaluations? Obviously they are mediated by different
5 concerns, but is there a strong association or are they
6 totally disparate?

7 DR. STERN: Well, I think a lot of it depends on
8 how controlled the situation is and both of those are
9 subject to both observer bias on the one hand and patient
10 Expectations on the other. So, for example, in just
11 clinical practice, how you approach the patient, whether you
12 have a smile on your face and look like things are going
13 pretty well and then you ask the patient how you are doing,
14 that gets you an entirely different response than if you
15 come in and you sort of have this slightly worried look on
16 your face about how are you doing.

17 So I think those are highly subjective. In my
18 practice, probably my patient's evaluation of how they're
19 doing probably depends on how well I slept the night before
20 to as much of an extent as the therapeutic effect. And in
21 terms of clinical trials--I mean, after all, what we're
22 really about when I treat patients with psoriasis is getting
23 them to a point where they're comfortable with it without my
24 twisting their arm.

25 But I am concerned about those kinds of

1 evaluations in clinical trials because it usually is very
2 clear who is getting placebo and who is getting drug. Anti
3 then the amount of swishiness is very large.

4 CHAIRMAN McGUIRE: Dr. Wilkin?

5 DR. KILPATRICK: I have a second question.

6 CHAIRMAN McGUIRE: Oh. Have your second question.

7 DR. KILPATRICK: Okay. And this comes back to Dr.
8 Rosenberg's emphasis of the dichotomous outcome in terms of
9 clearance, and I wanted to ask Dr. Srinivasan: From a
10 statistical point of view, are we not losing information if
11 we had an ordinal response which we could always degrade to
12 a dichotomous response? Will you have that information or
13 will we not have that information?

14 DR. SRINIVASAN: I know, Dr. Kilpatrick, where you
15 are coming from. You see that you are getting more degrees
16 of clearing when you look at the distribution. Well, what
17 does it matter to the patient or the doctor? He wants to
18 see complete clearing. What is the information that you are
19 carrying on by comparing the distribution to the patient?

20 DR. KILPATRICK: Again, I'm trying to reduce
21 sample size and increase the power of the test. Again, we
22 have had these types of discussions before, I know, and I've
23 always--

24 DR. WILKIN: We're getting all the categories.
25 All the categories are being reported to us. We're just

1 taking the top two categories and defining that as a
2 successful outcome.

3 What we want to know, especially we want to know
4 the very bottom one, which typically is the patient got
5 worse. That is important information for us.

6 CHAIRMAN McGUIRE: Do you have any comment?

7 DR. WILKIN: Actually, I had a question. I was
8 wondering how the photography was working? Are you
9 describing like epiluminescence or something to look at skin
10 markings? Because it sounded like that induration, plaque
11 thickness, is really the key element, that when that goes
12 away, then you can have this almost clear patient. That
13 would define the subset. And the question is: How does
14 photography help discriminate between that group and the
15 group just below it that has a minimally palpable--I mean,
16 that seems to be where the dividing line is, and I'm not
17 sure how photography helps it.

18 DR. STERN: In macular lesions, when you look--at
19 least it's my belief that when I look at them closely, as I
20 would with, say, a macro lens, I can tell when the skin
21 markings are more like the adjacent normal skin than when
22 they are not usual skin markings. And it's been my
23 impression, although I've never studied it systematically,
24 that taking close-up pictures, I can look, is there a
25 gradation other than pigmentation between the surrounding

1 normal skin and that patch, and say yes, no, and I think
2 that's doable.

3 DR. WILKIN: Yes. So in other words, the
4 photography is to pick up the superficial skin markings.

5 DR. STERN: Exactly.

6 DR. WILKIN: Thanks .

7 CHAIRMAN MCGUIRE: Dr. Rosenberg, you had
8 something?

9 DR. ROSENBERG: I just said, there's a paper by
10 Steve Feldman from Foman(?) Gray, published in the last two
11 years, in which he found quite a good correlation between
12 patients' assessment of how they were doing and how he
13 thought they were doing. And it turns out to be, I think, a
14 very useful addition to the work. I haven't read the paper
15 for a long time, but I've heard him give the talk, and I
16 believe it's been--I've seen it published.

17 CHAIRMAN MCGUIRE: Dr. Drake is going to have the
18 last question of the morning. We're going to break after
19 her question and reconvene at 1:00 p.m. There will be at
20 least one presentation in the open hearing before we proceed
21 with the questions.

22 Dr. Drake?

23 DR. DRAKE: One of the things, Jon, I wanted to
24 comment on the photograph. You know, at Mass. General in
25 the clinical investigations, you know, we've done a ton of

1 work on different types of photography, including polarized
2 photography and fluorescent photography. And what's very
3 interesting--and this work is published, most of it's
4 published, but one of the very interesting things on
5 psoriasis is that if you use polarizing filters, you can
6 remove the scale and see what's going on underneath the
7 scale instantaneously.

8 Further, even though the lesion may appear
9 clinically clear, with polarized photos you can often see
10 lots of stelanectasias (?) still remaining, or papillary
11 tips. You know, the little vessels in the papillary tips
12 are just quite visible. So there are very sophisticated--I
13 don't want to say very sophisticated. It's a matter of
14 putting polarized lenses on. Now it's commercially
15 available, by the way, so anybody now can buy these camera
16 set-ups.

17 But it's very useful in evaluating psoriasis to
18 use polarized photos because if you use the perpendicular--
19 if you use the filters parallel to each other, you
20 accentuate the surface markings, i.e, scale, and so you can
21 really get a better visualization of scale. If you put the
22 polarizers perpendicular to each other, you actually erase,
23 what you're doing is erasing the reflected light. So then
24 you get what's underneath the scale because the scale
25 basically is a reflection, and some of the light also gets

1 attenuated by being absorbed by the chromophores. So by
2 using the polarizers, you really eliminate the limitations
3 on the camera.

4 And if you stop and think about it for a moment,
5 when you evaluate a patient, we all use polarizing--we all
6 use light. We manipulate the optics of the skin because we
7 look this way and we look that way and we look up and down
8 and we have **our magnifying lenses**. All we're doing is
9 manipulating the optics on the skin. And now that can be
10 done basically with commercial photography. Those systems
11 are available. They can be purchased, and they're very
12 helpful particular in evaluating psoriasis because by which
13 you orient the filters, you can collect a lot of information
14 that's reproducible. So I wanted to point that out.

15 The second thing--and this relates to Dr. Hen-Sum
16 Ko's comment--I think you said that the eye--I wrote it
17 down, actually--the eye-brain is not good. In fact, we have
18 also published this work. We've also developed a technique
19 at Mass. General using diffuse **reflectant** spectroscopy as a
20 measure of **erythema**, and we did all the validation studies
21 on this. So it's work that's been totally validated,
22 published in the Journal of Investigative Dermatology in
23 1994. But much to our surprise, what we learned **is that**
24 this new diffuse **reflectant** spectroscopy is very good at
25 measuring erythema. It gives you an objective, quantitative

1 measure. It can also measure melanin. And what was
2 particular interesting to us, though, is it correlated
3 linearly with visual observations both clinically and it
4 also correlated with doppler measures.

5 So what we learned is that, although the diffuse
6 reflectant spectroscopy is actually more sensitive because
7 it can measure--it's more sensitive than what the eye can
8 do. Once you get into the range where the eye can see it,
9 the clinical evaluations of erythema correlated linearly
10 with this objective numerical measures. So there are some
11 new tools out there.

12 And then just finally, I wanted to make one
13 comment, and this has to do when we're looking at the
14 evaluation of patients with some of the newer, very potent
15 immunosuppressives that are now coming down the line. I
16 think the a la Rob Stern type follow-up work is absolutely
17 mandatory, because if we don't do follow-up on some of these
18 potent immunosuppressives, we're not going to have data on.
19 are there new cancers, are there new infections, are there
20 new everything. Because I'm very concerned that we've got a
21 disease that won't necessarily kill them, and we may kill
22 them with the treatment for the disease that won't kill
23 them. So I think you have to have long-term follow-up on
24 some of the potent oral immunosuppressives.

25 Thank you, sir.

1 CHAIRMAN McGUIRE: Okay. That's a good place to
2 stop, and we can reflect on the morning's business, and I'll
3 see you at 1 o'clock in the open session.

4 [Luncheon recess.]

1 the answer to that obviously is yes, but I think they really
2 want to know what the minimal entry conditions will be.

3 Who would like to deal with that? Dr. Lebwohl?

4 DR. LEBWOHL: We've already addressed the hazards
5 of scale and erythema. Moderately severe plaque thickness,
6 whatever the scale. On the 0 to 8 scale, it would be 4. On
7 the 0 to 3 scale, it would be 2. So moderately severe
8 plaque thickness.

9 CHAIRMAN McGUIRE: Area?

10 DR. LEBWOHL: Minimal area, I would vote against
11 requiring minimal area. If you have a 4 plaque thickness,
12 you have to have some area that can be looked at for
13 efficacy, and I think the best example I can show you is
14 that elbow I showed you, which is less than 1 percent body
15 surface area, but obviously disfiguring for the patient who
16 had it, and easy to assess whether that would respond to
17 therapy or not.

18 CHAIRMAN McGUIRE: Okay.

19 DR. DiGIOVANNA: When you say plaque rather than
20 papillae, you've already established at least one small
21 minimal area. We're talking probably not less than a
22 centimeter.

23 DR. LEBWOHL: Right.

24 CHAIRMAN McGUIRE: You're pushing.

25 [Laughter.]

1 DR. DiGIOVANNA: That's the way it is.

2 CHAIRMAN McGUIRE: Dr. Miller?

3 DR. MILLER: I think that as long as you define
4 your criteria, the minimal part of the severity could be as
5 low as you want it, because I think what we've seen today
6 and what we've seen in our studies is that most of these
7 products do not lead to complete clearing. That's obviously
8 our goal, but they don't lead to that. And what you see is
9 you see that dramatic loss of scale, and you see some
10 reduction of erythema, and you see some decrease in plaque
11 size. And then things just seem to level off, and you're
12 left with some activity. So that it's conceivable that you
13 would have a preparation that you say we want to go in and
14 we want to take something that is almost normalized, but you
15 still don't have normalization of skin lines. You know,
16 that would be an acid test.

17 So there might not be a minimal severity, but as
18 long as you define what you're looking at.

19 CHAIRMAN McGUIRE: Okay. I think you're sort of
20 easing into endpoints, and we're talking about entry right.
21 now .

22 Dr. Wilkin?

23 DR. WILKIN: I think what we're asking for is to
24 get the indication of psoriasis. Conceptually, a sponsor
25 could come in and ask for a subset of psoriasis that they

1 would define as being very minimal, and we could craft that
2 into the language in the indications section in the
3 labeling. So the question today really is more for the
4 usual kind of psoriasis.

5 DR. STERN: I probably shouldn't say this, but as
6 always, I will. I mean, one of the problems is, in fact,
7 you know, there are criteria for atopic dermatitis. There
8 are, in fact, no published criteria for what makes psoriasis
9 as opposed to seborrheic dermatitis, for example. And, in
10 fact, there is a group working on trying to come up with a
11 clinically useful definition of psoriasis that might be
12 applicable to clinical trials as well as epidemiologic
13 studies. So I think one of the things you have to think
14 about is, first, what makes psoriasis as a disease, what are
15 the clinical--the signs and symptoms that are sufficient to
16 make you reasonably confident that an individual has
17 psoriasis and not lichen simplex chronicus and not
18 seborrheic dermatitis and maybe not mycosis fungoides or
19 whatever. So that's number one, and I think maybe the
20 agency needs to perhaps be in touch with this group or other
21 groups and really come to a definition which--when I was
22 approached about this, I was amazed. You know, that's
23 right, there's no real workable definition of plaque-type
24 psoriasis.

25 The second is I think for clinical studies, you

1 know, it's one thing to say what should be the minimum that
2 you can use an agent for an individual if you are reasonably
3 confident because they have two pits in their nail, two
4 small plaques on their elbows, and pinking around their
5 gluteal cleft, and you say, boy, this sure looks like
6 psoriasis to me. It's one thing to say when might you use
7 an agent. It's another thing to say for purposes of
8 enrollment in a clinical study, what is a reasonable degree
9 or type of psoriasis. And there I think you want to get
10 above minimums. Because one of the problems is if you start
11 with very little, it's hard to measure change. And also
12 very little--you know, you ask a patient, and they say, oh,
13 yeah, it's been like that for a while, but, in fact, this
14 could be psoriasis that is regressing. Little bits are much
15 more likely, in my experience, especially small patches,
16 often are much more likely to respond to other things. So
17 it confounds the whole evaluation.

18 So it's one thing to say, you know, can you use--
19 if something is approved for mild to moderate psoriasis, can
20 you use it on minuscule psoriasis? Sure, if you think it's
21 worthwhile. But I think when you're designing clinical
22 trials and want to interpret them, I would set the bar
23 somewhat higher than has been suggested with respect to
24 some--and I have no advance--you know, I can't give you
25 numbers in terms of size and number, but I would set it in

1 terms of certain minimums, either combinations of sizes and
2 numbers of lesions symmetrically distributed, and I think
3 you need to think about that. But I wouldn't say if you had
4 two patches this small that you're an appropriate candidate
5 for a clinical trial for a prescription medicine. And I
6 think you want to think about what you need.

7 CHAIRMAN McGUIRE: Well, you're really touching on
8 the area, again, and I think the agency would like to know
9 how strongly we feel about area. It's true that an
10 individual could have a very small area involved and be
11 quite disturbed by it and be strongly motivated to therapy.
12 But that might not be a good subject for a clinical trial.

13 DR. STERN: That's exactly my point, yes.

14 CHAIRMAN McGUIRE: I thought that's what you said.
15 Can we move to endpoints, Jon?

16 DR. WILKIN: Yes.

17 CHAIRMAN McGUIRE: Good. Would a dichotomous
18 outcome for global evaluation be preferable to an all-
19 category comparison ("edge up") as the primary endpoint?

20 Well, you see, I didn't understand that question
21 earlier today, and I think I do now. And then the issue is
22 whether there should be an ordinal evaluation or whether
23 it's going to be a yes or no. And I think what I heard this
24 morning was that the data would be collected, and then it
25 could be dealt with in a dichotomous fashion if that were

1 appropriate .

2 Is that what you heard, Jon?

3 DR. WILKIN: I think so. In other words, in terms
4 of global, we would have all of the categories, but we would
5 only use the top two to find success.

6 In addition to that, we could have scoring for the
7 three cardinal signs: erythema, plaque thickness, and
8 scaling.

9 CHAIRMAN McGUIRE: And area.

10 DR. WILKIN: And--well, that's one of the further
11 questions down, how to craft area into this. I gather it's
12 the committee's view--I know it's your view--that the more
13 lesions somebody has, they are likely not to respond as well
14 if someone has one or two lesions. That was in one of your
15 early slides, extent of involvement. And so really, one
16 would have to stratify if we use lots of different areas.
17 [s that fair or--

18 DR. STERN: That's right. I think there's an
19 association between extent of disease and difficulty of
20 clearing, so it isn't a fair test to compare two patches of
21 the same size, one on an individual who has dozens or
22 hundreds of such patches, and another on an individual who
23 has a solitary patch. You know, it's something that's
24 correlated. It's not always the case, obviously.

25 DR. LIM: But the other factor along that line

1 also is the anatomic location, which has been mentioned
2 before. I'm thinking specifically about the scalp, for
3 example. If you have treatment for scalp psoriasis, clearly
4 the area is not going to be--it's going to be much smaller,
5 and that has to be taken into consideration. The response
6 could be very, very different because of the anatomic site.

7 CHAIRMAN McGUIRE: Dr. Kilpatrick, you spoke to
8 the issue of the ordinal evaluation versus dichotomous, and
9 I know you've spoken on that issue before. Maybe you'd like
10 to--

11 DR. KILPATRICK: I'd like to come back to that,
12 Toe, if I may. I'd like to return to what I now understand
13 is the design of the trial. We now agree that it's a two-
14 arm study, and it seems to me that we still will have a
15 before and after comparison. Clearing is one way to do
16 that, so we have a comparison between clearing in one arm
17 and clearing in another arm. But I would suggest that if we
18 go for other types of evaluation, we may have, in effect, a
19 difference of differences, before to after in one arm, to
20 before minus after in the other arm. So it gets a little
21 bit more complicated, and in that sense more robust.

22 But in my discussions with Dr. Srinivasan and
23 others, I am content to accept a dichotomous outcome. I'm
24 not content to accept that clearing is the best modality for
25 the dichotomous outcome.

1 CHAIRMAN McGUIRE: Well, there was discussion this
2 morning that 75 percent would be a number that might be
3 identified as a successful outcome. Do you want to speak to
4 that ?

5 DR. ROSENBERG: No, that's wasn't--

6 DR. LEBWOHL: Well, I did suggest that.

7 CHAIRMAN McGUIRE: Could you speak to that, Mark?

8 DR. LEBWOHL: Yes. You know, I am concerned--if I
9 can suggest a hypothetical drug to you, if we have an oral
10 or topical agent that does not clear psoriasis but results
11 in what every investigator would call dramatic improvement,
12 75 percent--and 75 percent is not edging up. Edging up
13 means you're going from plaque of moderate severity to mild
14 severity or severe to moderate. Seventy-five percent is
15 severe to mild or severe to clear. So that's not edging up.

16 And I am concerned that if we have a drug that
17 results in no clearing but is clearly beneficial for
18 patients with psoriasis, that drug will never see the light
19 of day if it's an absolute requirement that even a tiny
20 percentage clear.

21 Now , in the dichotomous evaluation, you know, you
22 can look at two different categories of response, but if it
23 is an absolute requirement that a proportion of patients
24 clear, we will end up finding ourselves without some drugs
25 that would have otherwise been very helpful to our patients.

me

1 CHAIRMAN McGUIRE: You could imagine a situation
2 in which Agent A totally cleared 10 percent of the patient
3 population and a vehicle only cleared 3 percent. But it's
4 still not worth it. You'd far rather have Agent C that
5 cleared 90 percent of the patients 75 percent, if I think
6 we're on the same track.

7 Dr. Rosenberg?

8 DR. ROSENBERG: No, I don't think so. I think
9 that the speakers this morning made it clear, Dr. Stern
10 particularly. Patients really want to be all better, that
11 it's all gone. That's a very big difference, and it's worth
12 shooting for. And things we know about psoriasis--and this
13 is in print for almost a hundred years now. If you can
14 succeed in getting the patient totally, absolutely, utterly
15 clear, which usually involves getting them better and then
16 sending them to the beach and so forth, so that you look at
17 them, they look at them, nobody can see where it was,
18 they're much more likely to stay clear for a lengthy period--
19 -I didn't say cured--than if you get them much better.

20 It's worthwhile getting that last little bit to go
21 away. This is discussed, this is clinical wisdom, and it's
22 true. I think we ought to retain this clear or nearly clear
23 as an entity. You don't need to require it to pass the bar
24 of approval, but--

25 CHAIRMAN McGUIRE: Bill, that's in your practice

1 where you're using three agents or four agents and
2 everything you have. And if we're talking about a sponsor
3 with a single agent that wasn't to be tested, those may not
4 be the right hoops for him to jump through.

5 DR. DRAKE: But just a clarification. I don't
6 think--Bill., help me with this, but I don't think he's
7 saying that totally clear is the bar. I think he's saying
8 that information is useful to collect, but it's not
9 necessarily the bar. Is that what you were saying?

10 DR. ROSENBERG: Exactly. I think if it's better
11 than placebo and edges up, that's with everything else out
12 there, much of what else out there is. I don't think it
13 should be held, certainly **topicals**, to a much more stringent
14 standard than presently approved things. Maybe--I don't
15 know that. If it's better than placebo, I think that's the
16 regulation that they have to follow. But I'm saying the
17 information on clear changes things, and I think we ought to
18 know it.

19 I think it's not that crucial. If you're going to
20 approve them, anyway, if a company's got something that's
21 good enough to clear people, we'll do some Phase IV studies
22 and let the world know about it. But, still, it would be
23 nice to know up front. And I think it relates also to
24 decisions about safety when you're constructing your
25 equation and risk.

1 CHAIRMAN McGUIRE: Dr. DiGiovanna?

2 DR. DiGIOVANNA: I just want to clarify one issue
3 in my own mind. By clear, we mean that a treated lesion or
4 a pair or sets of lesions are clear? Or are we talking
5 about with a systemic treatment that the patient is clear of
6 all lesions?

7 DR. WILKIN: Yes.

8 [Laughter.]

9 DR. DiGIOVANNA: Thank you.

10 DR. WILKIN: I thought that was a good FDA answer.

11 Really, you're free to define that. I really
12 think we've heard two settings. One would be a certain
13 percent of lesions would need to fall into the win category,
14 and then I think we've heard the other view that all would
15 need to meet some sort of minimum that might be a lower bar,
16 if you will,

17 What Hen-Sum, of course, had in his presentation,
18 what we've currently been thinking about, is having a
19 complete clear category and reporting it in the clinical
20 studies section of the labeling, and also an almost clear,
21 but that's the one that we're having difficulty with. How
22 does one actually define almost clear? And 75 percent, we
23 have struggled with that internally in the agency. We don't
24 really know what that means.

25 DR. DiGIOVANNA: That's good.

1 DR. WILKIN: We were hoping for--and I think also
2 you were talking about induration, plaque thickness, may be
3 the most important element. Maybe that could be used to
4 define the almost clear category. But if we could have
5 something like that that would be the same from one
6 investigator to the next--

7 CHAIRMAN MCGUIRE: Dr. Stern and then Dr. Lebwohl.

8 DR. STERN: I think we have to separate out how
9 we're using percentages. To me, almost clear means flat but
10 essentially non-palpable, not appreciably scaly, but it's
11 not normal skin. It has pink. It has not normal skin
12 markings.

13 And I think that to me is almost clear and is
14 what--if an agent doesn't get you to that, it's really not
15 doing very much. And that to me is there. Then you--how I
16 like to look at percentages, I don't think it's fair to say,
17 all right, of the treated lesions, did they all get to that
18 criteria? My criteria, when I talk about percentage, is to
19 say of the treated areas for topical agents, or for a
20 systemic agent of all areas, did a certain proportion of the
21 areas we would have expected to have been exposed to the
22 agent, in fact, reach this. I don't think you can expect
23 that every patch is going to get better. We've talked about
24 anatomic differences. There's going to be application
25 differences, et cetera, et cetera. But of the index

1 patches, can you say, yes, you know, 75 or 80 percent of
2 those areas that were treated, in fact, reached this level
3 or, in fact, having no more level, now being on the level,
4 and only differing in terms of color and texture, not scale
5 and not being very scaly. So that's how I look at almost
6 clear, but I don't think you can say, gee, every single
7 patch is absolutely flat. Of the body area, what proportion
8 of them have gotten to that area?

9 CHAIRMAN MCGUIRE: Rob, that's still stringent,
10 because we don't have very many monotherapies that carry us
11 to that point.

12 Mark, you, and then John, and then, Bill, do you
13 want to--

14 DR. ROSENBERG: Yes, just one question.

15 DR. LEBWOHL: My question would be: How is the
16 agency going to use it? Is it going to use it as a
17 requirement for approval or as a source of information for
18 physicians and patients? It's a very useful source of
19 information for physicians and patients, which is what Bill
20 Rosenberg said, and I agree. And some of the data that's
21 out there can confuse you about how much to expect out of a
22 drug, and if this information is available, it will be
23 helpful.

24 On the other hand, if we are going to require
25 clear or almost clear for approval, a lot of drugs we have

1 now won't do that. A lot of drugs that are approved today
2 do not do that.

3 CHAIRMAN McGUIRE: John, does that deal with--

4 DR. DiGIOVANNA: Well, no, I agree with that, but
5 that still doesn't deal with my issue. I want to get back
6 to Rob for a second. I'm not quite sure what you're talking
7 about. I think we're still muddling the issue if we haven't
8 defined what we mean by clear. I think that you need to
9 look upon a grading system to define what is required for
10 approval in a different way, whether you're talking about a
11 systemic treatment or whether you're talking about a topical
12 local treatment. And if you're talking about one lesion and
13 that lesion has to be clear, that's one issue. If you're
14 talking about a total body treatment, then how do you come
15 up with a grading scale that incorporates how many of those
16 lesions are going to be near clear and how many have to be,
17 and how are you going to standardize that across different
18 centers. I think you have to do that in a different way.

19 Do you understand what I'm asking?

20 DR. STERN: I think so. I think the criteria for--
21 --and let's not use the word "clear." Let's use the word
22 "substantial clinical improvement." Criteria for me is a
23 flat patch. That's a substantial clinical improvement.

24 DR. DiGIOVANNA: I understand what you're saying
25 with respect to one lesion. What I don't understand is how

1 you take into account or how you quantify with a systemic
2 treatment an individual who has 60 lesions and several of
3 those lesions are clear and several of those lesions haven' t
4 moved as much as you would have liked. How do you--
5 **something is clear, if you look at that one lesion, but--**

6 **DR. STERN: And that's where percent comes in.**

7 **DR. DiGIOVANNA: --if a patient was clear, 90**
8 **percent of those--**

9 **DR. STERN: That's where I think about percent.**

10 Of the original areas that you thought your agent might have
11 an effect on, given either where it was applied, how it was
12 used, what proportion of the original lesions reached
13 meaningful clinical improvement. And that's an area issue,
14 and it has all the problems of area measurement It's
15 another reason why photographs are perhaps something you
16 want to use or perhaps index areas or index lesions so that
17 those can be measured more accurately.

18 But , in fact, at the end of time, the one problem
19 is if you don't have baseline photographs, if some skin is
20 completely normalized, you underestimate the extent of
21 effect, but for the more usual treatment that doesn't
22 completely clear you, you can see which patches are flat and
23 which aren't flat. And you can do a rough proportion of
24 those who reached essentially substantial clinical
25 improvement versus the proportion that didn't. And that's

1 the percent I'm talking about.

2 CHAIRMAN McGUIRE: I think you have--no. I was
3 going to say you've made it clear, but that's not--you've
4 made it--I understand what you're saying. And Dr. Rosenberg
5 has **been very patient.**

6 DR. ROSENBERG: Thank you. I think the
7 **comparisons and so forth** now are what golf was like, you
8 know, when Scotsmen had tree limbs and would hit the ball
9 and come back and say, I hit a long one, right into the
10 hole, and then they started putting numbers on and we could
11 find out who the best players were. And some treatments are
12 better than others, and, you know, I'd be perfectly happy
13 with the Karnofsky scale, grade 0, no signs, no symptoms, no
14 prescription, no return appointment; grade 1, no signs, no
15 symptoms, prescription and appointment; grade 2 and so
16 forth, so forth. I mean, let's do it. There are treatments
17 that are that good, And if the other treatments aren't that
18 good, we ought to know that, too.

19 I'm not inventing this. This has been around.

20 CHAIRMAN McGUIRE: Dr. Kilpatrick?

21 DR. KILPATRICK: I want to come back to Dr.
22 Stern's recommendation for physician evaluation, in effect,
23 **and** go away from percentages as such to just what Bill is
24 saying, to an ordinal ranking of good, better, best, and all
25 the rest of it. That seems to me, even though it's

1 subjective and given that it's based on standardized
2 photographs before and after, that seems to me the better
3 way to go than the percentage. No? You disagree?

4 DR. STERN: I disagree because traditionally it
5 has not been photographic by a blind observer, and in most
6 of these trials, it's fairly clear in a high proportion of
7 patients who's on active and who's on placebo, and there's
8 so much potential observer bias that I think it's hard--it's
9 very hard to do it.

10 I think you have less bias when you force people
11 to say has it met a certain criteria that's reasonably
12 objective; and if so, how much of it has met these criteria.

13 DR. ROSENBERG: How do YOU know who's on the
14 active--

15 CHAIRMAN MCGUIRE: Bill, speak into the
16 microphone.

17 DR. ROSENBERG: How do you tell who's on the
18 active?

19 DR. STERN: Well, certainly placebo, if things
20 have any activity--there's a difference between patients,
21 but most of these agents--first of all, it depends what
22 kinds of agents. You know, we have unbinding from
23 irritancy with topical retinoids and Dovonox. We have
24 differential effects on inflammation. You can tell in a
25 high proportion of patients. And with effective drugs you

1 can tell right away because they're really working.

2 DR. WILKIN: Dr. McGuire?

3 CHAIRMAN MCGUIRE: Dr. Wilkin?

4 DR. WILKIN: It's in all the dermatology textbooks
5 that psoriasis comes and goes and there are certainly
6 spontaneous remissions. But, you know, the number of
7 patients who have achieved complete clearing while they've
8 been on placebo during the study is minuscule. I mean, it's
9 very, very tiny. So we're really not talking about a large
10 proportion of the patients who are on active need to achieve
11 **complete clearing or that lesser category. It's that that**
12 **proportion just needs to be statistically superior to the-**

13 CHAIRMAN MCGUIRE: I agree, but one of the points
14 that's being made is that the patients who are on active
15 agent do not achieve 100 percent clearing if we're talking
16 about return to normal skin markings, loss of discoloration.
17 There are no footprints left. It's gone. That's unusual
18 for monotherapy.

19 DR. WILKIN: And that's why Hen-Sum had in his
20 overheads the notion of going to a lesser category where
21 there really is not complete clearing. That would resonate
22 best, you know, with the reviewers in the division. This is
23 not an infectious disease. It's--okay. Dr. Rosenberg
24 raised his eyebrows on that.

25 CHAIRMAN MCGUIRE: Did he raise his hand?

1 Dr. Drake?

2 DR. DRAKE: Well, Jon, I think I have to agree
3 with you. I think that if there is complete clearing, it
4 should be noted on the case report form so that data can be
5 collected, because it's interesting and it would be fun to
6 know and it would important to know.

7 On the other hand, I've done too **many studies;**
8 it's unusual to see patients get completely clear, but you
9 can have a lot of patients who get a lot better. And I
10 think that happens in just everyday practice. You have
11 patients you play around with. You do this for a while and
12 you do that for a while, and the game is to try to keep them
13 better. I don't think anybody who treats very psoriatic
14 patients uses a monotherapy. I think we all mix and match a
15 little bit to try to get them better.

16 So I think we can try to get numbers fixed so
17 ideally that we bog down in that and forget the big picture.
18 And the big picture, Is the patient getting better and is
19 the patient happy? I guess that's where I would come from.

20 CHAIRMAN MCGUIRE: Jonathan?

21 DR. WILKIN: Actually, part of it may be that
22 we're confusing two points. One of it is the kind of
23 information we want to craft into the labeling we think will
24 be useful, and the other is the bar to get to approval. And
25 just to mention what we do with antifungal, we have what we

1 think of as regressing subsets. The largest number that
2 would be reported in the clinical studies section for an
3 antifungal would be that proportion of patients who had
4 mycological cure, negative KOH, negative culture. The next
5 subset, which would be smaller, because they would have to
6 mycological cure, but they also would have either clinical
7 cure--that is, no signs or symptoms, or just very low grade
8 signs and symptoms, scores of 1-plus, 2-plus, 3-plus, that
9 sort of thing. And then the tiniest subset, which is in the
10 middle, those are the people who are completely clear
11 clinically and also have mycological cure.

12 Now , in terms of tinea **pedis**, we're willing to go
13 down and include the first two categories, those who have,
14 you know, the clinical cure plus mycological cure; the
15 second category, those that have just a couple of residual
16 signs and mycological cure. But we don't count mycological
17 cure towards giving approval.

18 In the case of psoriasis, what we were thinking is
19 we would list in the clinical studies section that
20 proportion of patients who had complete clearing, and then
21 we would also list the proportion of those who didn't have
22 complete clearing, but we would define what that second
23 category was, hopefully in morphologic terms rather than
24 percents, and it might even have some sort of tag with it
25 that said at least half of the lesions, or something like

1 that, achieved this kind of morphologic endpoint. And all
2 of that, both of those groups together would be useful for
3 approval, but we could separate them out for information
4 purposes for the patient and the clinician in the clinical
5 study section of the labeling.

6 CHAIRMAN MCGUIRE: Dr. Kilpatrick?

7 DR. KILPATRICK: Dr. Wilkin has gone some way
8 towards answering my problem, which is purely statistical,
9 and the FDA statisticians may care to respond to it.

10 I'm coming back to the issue of using as primary
11 endpoint the percentage of patients which clear, by whatever
12 definition. Dr. Wilkin has said that under the inactive or
13 placebo treatment, virtually nil, 0 percentage will clear,
14 and if a tiny percentage like 5 percent in the active arm
15 clear, then we're comparing 5 percent to 0 percent. That
16 requires a much larger sample size because of a phenomenon
17 of the binomial distribution, a much larger sample size than
18 to compare a 5 percent difference at the 50 percent level,
19 that is, between 50 percent and 45 percent. So I don't
20 know--that's one of my concerns. Sriniv or Jon?

21 DR. WILKIN: That actually would be true if we
22 were only thinking of complete clearing.

23 DR. KILPATRICK: That's true.

24 DR. WILKIN: But the proportions are a little
25 larger when we include the almost clear, and--

1 CHAIRMAN MCGUIRE: Yes, I don't think at a
2 practical standpoint, I don't think a sponsor will be
3 dealing with an agent that has 5 percent clearing. I mean,
4 I don't think it's going to be a headache for us.

5 DR. SRINIVASAN: I was planning to say the same
6 thing that Dr. Wilkin said. We can go lower down and add
7 the numbers, and then compare them.

8 CHAIRMAN MCGUIRE: Okay. I think we have slipped
9 through 2.2. 2.1 was, Would a dichotomous outcome for
10 global evaluation be preferable to an all-category
11 comparison ("edge up") as the primary endpoint? Then 2.2
12 was, If the answer is yes to question 2.1, what should the
13 successful outcome be in a dichotomous global evaluation?
14 And there we talked about percentage of lesions achieving
15 some acceptable level of improvement.

16 Should the three cardinal signs--whenever you read
17 a question like this, you know that the answer is no.

18 [Laughter.]

19 CHAIRMAN MCGUIRE: It worked on the SATS. That's
20 all I--

21 [Laughter.]

22 CHAIRMAN MCGUIRE: Should the three cardinal
23 signs--plaque elevation, scaling, and erythema--carry equal
24 or different weights? How should their scores be combined
25 as another primary endpoint?

1 Fred, why don't you hit that? Eye contact.

2 DR. MILLER: Eye contact. I think there's been a
3 lot of discussion about this, and I think the first thing is
4 the scaling can certainly be eliminated with very simple
5 techniques. It's been observed with Vaseline or whatever.
6 So it's difficult to assess that a major weight.

7 Erythema varies from day to day and from times
8 within the day, so that we're pretty much left with plaque
9 elevation, which is the gold standard. You know, how much
10 is the plaque reduced? How rapidly is it reduced? And is
11 it flattened completely and is there normalization of skin
12 markings?

13 CHAIRMAN McGUIRE: I agree with that. Is there
14 disagreement on--yes, Eva?

15 DR. SIMMONS-O'BRIEN: No disagreement. I agree
16 with Dr. Miller, and I just wanted to make this point. I
17 think that--and I'm always telling the residents--erythema
18 is relative. First, I agree with Dr. Lebwohl's comment on
19 getting rid of the scale. You can sometimes mask the
20 erythema or even enhance it because you've gotten rid of the
21 scales. So that becomes very tricky. But erythema is--most
22 of my residents think bright red/pink, and I would argue
23 that depending on the patient's skin type, that might vary
24 to be violaceous brown-purple. But it's still erythema.
25 And unless you're used to seeing that and you're used to

1 judging how that particular erythema resolves in that
2 particular skin type, that can be very skewed.

3 So you can't really hang your hat on erythema too
4 much because it's such a broad spectrum.

5 CHAIRMAN MCGUIRE: What I have heard is that we've
6 downgraded scale because it's so easy to deal with, and we
7 have put erythema in a category of--it's somewhat
8 treacherous because it can be revealed by the reduction of
9 scale, and so we are depending greatly upon the thickness of
10 plaque, which leads us into: How should their scores be
11 combined as another primary endpoint? It sounds like we're
12 putting most of our weight on plaque elevation.

13 DR. KILPATRICK: Joe?

14 CHAIRMAN MCGUIRE: Yes, Dr. Kilpatrick?

15 DR. KILPATRICK: I'd like to ask a question.
16 There are multivariate statistical techniques which enable
17 us to optimally weight different categories to discriminate
18 between different classes of patients, for example. Has
19 this ever been done for psoriasis in terms of finding an
20 optimal weighting system so that PASI is not just--you just
21 don't add everything together but you actually combine these
22 in an optimal way to discriminate between this type of
23 patient and that type of patient?

24 DR. STERN: What's the dependent variable?

25 DR. KILPATRICK: There is no dependent variable

1 here. It's like a principal components analysis or
2 something like that where you can find an optimal--
3 discriminative function analysis, something like that.

4 Srini, do you want to pick up?

5 DR. SRINIVASAN: I have not heard of it.

6 CHAIRMAN MCGUIRE: Dr. Drake?

7 DR. DRAKE: This is more of a question. You know,
8 I--

9 DR. KILPATRICK: Where did my answer go?

10 DR. DRAKE: I'm not answering it. You want--

11 DR. KILPATRICK: I want an answer.

12 DR. DRAKE: Well, then, let somebody answer it
13 first, and then I'll ask my question.

14 DR. KILPATRICK: There's nothing in the literature
15 with regard to this?

16 CHAIRMAN MCGUIRE: I think no one cared to answer
17 your question.

18 [Laughter.]

19 DR. DRAKE: Because we didn't know it.

20 CHAIRMAN MCGUIRE: Dr. Drake?

21 DR. DRAKE: When we say that everybody sort of
22 zeroed in on plaque as the gold standard, I think that's
23 fine. I guess this question assumes that you've got plaque-
24 type psoriasis. In fact, if you're dealing with
25 erythrodermic psoriasis or if you're dealing with hands,

1 like that picture that either Mark or Rob showed with just
2 the hand, there's no plaque, and yet that patient is more
3 severely disabled than anybody with 4-plus plaque.

4 I guess this whole thing reminds me of trying to
5 herd cats here today. You know, you keep trying to--the
6 questions keep trying to herd us to get us to give you an
7 answer, and, well, yeah, this is true, but three cats go
8 this way and the fourth cat pops out this way, and it's just
9 hard.

10 I think you have to define the types of psoriasis
11 before you determine what the cardinal sign that you monitor
12 is. In other words, if it's erythrodermic psoriasis, then
13 what you've got to monitor is erythroderma. If it's a
14 locational psoriasis, I think you have to monitor the
15 location and the primary feature that occurs at that
16 location.

17 CHAIRMAN MCGUIRE: I thought that was our charge,
18 to deal with chronic plaque psoriasis. I thought that's
19 what you were giving us.

20 DR. DRAKE: Well, okay.

21 CHAIRMAN MCGUIRE: So we're not dealing with
22 counting the number of pustules on a palm.

23 DR. DRAKE: Well, but not necessarily, because the
24 very next question says--on bony prominences. Now, a lot of
25 the stuff on bony prominences is not a plaque, and that's

1 why I assumed we weren't just--

2 CHAIRMAN MCGUIRE: You missed one.

3 DR. DRAKE: But , I mean, on 2.5. If you go down
4 to 2.5, you're saying, Should there be a stratification for
5 certain lesions? Well, very frankly, over bony prominences,
6 it's not a plaque. Over bony prominences, it can be
7 erythema. You can have a lot of scale.

8 I guess I'm still confused over what we're doing
9 here, then, obviously.

10 CHAIRMAN MCGUIRE: Well, okay. But let's deal
11 with 2.5 when we get to it, and let's deal with 2.4, since
12 that is the next one.

13 DR. DRAKE: The answer is yes.

14 CHAIRMAN MCGUIRE: Okay.

15 DR. KILPATRICK: I'd like to return to 2.3.

16 CHAIRMAN MCGUIRE: Now , wait a minute, Jim.

17 [Laughter.]

18 CHAIRMAN MCGUIRE: Okay. Return to it but let's--

19 DR. KILPATRICK: Again, how should the scores be
20 combined as another primary endpoint? I want to come back
21 to PASI because one of the speakers made the point about the
22 inequivalence of changes at one level of PASI score and
23 another level of PASI score. Again, there are
24 transformations . You can make transformations of a score
25 like that to make those approximately equal. Basically,

1 again, I'm talking about mathematical manipulation of a
2 combination of scores like PASI.

3 Mark, do you want to--

4 DR. LEBWOHL: Yes, well, several of the
5 alternatives that I showed do precisely that. In other
6 words, instead of incorporating entire body area
7 calculations, which are what we have in a PASI score, you
8 can have either target lesions or a limited number of
9 lesions that constitute your baseline, and then you evaluate
10 those on either 0 to 8 scales or 0 to 3 scales, and you come
11 up with your ordinal, with your line, degree of improvement.
12 so you can have 50 percent improvement and quantify that, or
13 you can have 75 percent and quantify that.

14 That is subject to some of the criticisms that
15 were raised earlier in that there is an eye-brain disconnect
16 where you don't remember what the patient started out with,

17 There are some solutions to that. You suggested
18 one of them, which is a bilateral comparison trial, which we
19 don't do in Phase III trials. That's an excellent solution,
20 by the way.

21 Photography is an excellent solution as well,
22 where you have a photo of the baseline, so you're not
23 relying on your memory as much. There are flaws with that
24 as well, such as getting your photo back in time.

25 But the point is that there are modifications of

1 PASI that we currently use that, frankly, I find vastly
2 preferable to PASI scores.

3 CHAIRMAN McGUIRE: Yes, I think no one is
4 satisfied with the clinical fidelity of PASI, and something
5 else needs to be engineered. And what we heard in Mark's
6 presentation this morning was different instruments that
7 have been designed to do just that.

8 Are we finished with 2.3, Jim?

9 DR. KILPATRICK: Thank you, sir.

10 CHAIRMAN McGUIRE: Good. Dr. Drake tells me that
11 the answer to 2.4 is yes. If so, how?

12 Who would like to speak to that?

13 DR. LEBWOHL: I will say--you know, someone asked
14 earlier today if we have to do double-blind placebo
15 controlled trials, and this is the reason, because you're
16 counting on, if you have 200 patients and one of the
17 patients you treat has only inverse psoriasis, has axillary
18 lesions, those clear very quickly and very easily, even with
19 placebo. And you're counting on having large enough numbers
20 of patients that that separates out, so that the same number
21 of placebo axillary lesions would be the same number of
22 active axillary lesions.

23 One of the real hazards of the complete clearing
24 is you can clear axillary psoriasis with petrolatum. And,
25 again, I'm getting back to that worry about us ending up

1 with--if you're using that for informational purposes, that
2 is excellent and will add to the value of what you're doing
3 for the last consumer, which is the patient and the
4 physician who prescribes that drug, But--

5 CHAIRMAN McGUIRE: You know what? It just
6 occurred to me that English is such a treacherous language.
7 I read 2.4 as should the area, in terms of square
8 millimeters, of involvement be included in the analysis, and
9 you're reading area as location.

10 DR. LEBWOHL: Oh, you're absolutely right . I'm
11 sorry.

12 CHAIRMAN McGUIRE: That's a funny--

13 DR. DRAKE: I read it the same way you did.

14 DR. WILKIN: Dr. McGuire?

15 CHAIRMAN McGUIRE: Yes?

16 DR. WILKIN: We were hoping to capture anatomic
17 regionality, which--

18 [Laughter.1

19 DR. WILKIN: In 2.5, the next one.

20 CHAIRMAN McGUIRE: That's what I perceived.

21 DR. WILKIN: And so area of involvement here, it
22 would have been better if we had body surface, you know,
23 percent body surface area involvement, something like that.

24 DR. STERN: The answer is still yes.

25 CHAIRMAN McGUIRE: So in 2.4, "area" is being used

1 in the traditional sense. And then the question is: How do
2 we factor it in? And it's got to be factored in. I'm not
3 sure if we can settle that right now.

4 Henry?

5 DR. LIM: Yes, I'm not sure whether I could answer
6 that completely, but I think the answer is I would agree
7 that absolutely we have to factor it in as to how big an
8 area of involvement it is. But assuming that, again, we are
9 dealing with only stable plaque psoriasis, guttate
10 psoriasis, are we supposed to consider that, for example,
11 because that is completely different. So as long as we are
12 dealing with stable plaque-type psoriasis, sure, I think it
13 has to be included.

14 DR. KILPATRICK: Yes, but it cannot be considered
15 only on its own, surely. Surely location is the point--

16 DR. LIM: Oh, no. I'm answering only specifically
17 2.4, area in terms of centimeters squared.

18 CHAIRMAN McGUIRE: Okay. So the answer to 2.4 is
19 yes. We're not sure what the coefficient should be, but it
20 clearly is important. And we're now at 2.5, Should there be
21 stratification for lesions according to their location,
22 according to anatomic site?

23 DR. KILPATRICK: May I have a definition of
24 stratification? What does stratification mean? It means
25 something to me as a statistician, which may not mean--is

1 that what we mean?

2 DR. SRINIVASAN: By anatomic lesions.

3 DR. STERN: Or separate consideration, is that
4 what you mean?

5 DR. KILPATRICK: Are we meaning matching patient
6 in one arm with a patient in another arm with the same type
7 of axilla involvement, or what? Is that stratification?

8 DR. LEBWOHL: There are certain areas--I'm sorry.
9 I shouldn't use the word "area." There are certain sites
10 that respond much more readily than other sites. And if you
11 treat intertriginous sites, you will achieve clearing,
12 sometimes even with placebo.

13 On the other hand, if you treat elbows and knees
14 or shins, which are notoriously difficult to treat, it is
15 much more difficult to clear patients.

16 DR. KILPATRICK: Then, to follow up, we're
17 talking--I'm coming back to the design again. We
18 conventionally talk about randomly allocating patients to
19 one arm or the other arm. But are you saying, sir, that we
20 may need to match patient with patient in terms of location?

21 DR. STERN: But randomization should take care of
22 that, and I guess what should take care of the problem of
23 anatomic site is I think intertriginous and facial psoriasis
24 should probably be considered, for stable plaque psoriasis,
25 sites not of interest for most of these products. So that's

1 sort of an exclusion.

2 I think one should--personally, you know, when I
3 think about treating psoriasis and success, another
4 exemption I sort of give myself is elbows, knees, and lower
5 sacral plaques, because I don't expect response there. I
6 think you don't necessarily want to write that into the
7 protocol. I think any company that does a study where they
8 concentrate on elbows, knees, and **sacral** plaques have hired
9 the wrong consultants. But randomization should take care
10 of most of the other problems. And I think you can say that
11 specifically if you can exclude certain areas in your
12 assessment of improvement because we know that these are
13 there, similarly you can't get credit for certain areas
14 because we know anything makes these better And that's how
15 I deal with this, that and the power of numbers and
16 randomization, how I would deal with this problem.

17 DR. KILPATRICK: I would just like to add to that
18 while I completely agree that we don't--they're not mutually
19 exclusive. We can have both stratification or matching and
20 randomization, block assignment .

21 DR. STERN: I don't think we have to go to
22 stratification.

23 CHAIRMAN McGUIRE: Okay. Question 2.6, To what
24 extent can quality-of-life assessment be used in the
25 evaluation of success in the treatment of psoriasis?

1 Bill, I was going to ask you to speak on that.

2 DR. ROSENBERG: Thank you. Quality of life, of
3 course, is especially all its own. We have authorities in
4 the room with it, but I think it would be simpler--I would
5 suggest that perhaps as an alternative the agency would
6 consider just the patient's assessment of the efficacy of
7 treatment. But I think that's crucial, what the patient
8 thinks of how well the treatment worked on some kind of a
9 wonderful, good, fair, disappointing scale, something like
10 that.

11 CHAIRMAN McGUIRE: I think that the instruments
12 that have--I think you're right, but I think there are more
13 precise instruments for measuring self-esteem and- -

14 DR. ROSENBERG: That's different.

15 CHAIRMAN McGUIRE: --and socialization--well, it
16 has to do with quality of life.

17 DR. ROSENBERG: I know, but--

18 CHAIRMAN McGUIRE: I mean, quality of life means
19 more than just how do you feel about the treatment. It
20 means : Are you going back to work? Are you going to the
21 beach? You know, patients say, "I'm wearing short-sleeve
22 shirts, " and it never occurred to me that wearing a short-
23 sleeve shirt was a big deal. But to that person, it's a big
24 deal .

25 I don't know how you score short-sleeve shirts,

1 but there are a lot of issues around that.

2 Mark, you've thought a lot about this, and you've
3 tried to--you beat your head against that wall a lot.

4 DR. LEBWOHL: Well, you know, I am very cautious
5 about including it as a criterion for approval, and I'm not
6 even sure if we should yet be doing it as a criterion for
7 evaluation. I have dealt with this with great difficulty.
8 Most of the studies that have tried to line up pretty
9 effective treatments versus quality of life have yielded
10 negative results. Most of them have. And, in fact, Dr.
11 Stern has published one study which looked at that, and some
12 of the best treatments we have did not affect quality of
13 life even though they are clearly dramatically effective
14 treatments.

15 I'm not sure that the fault yet is with the
16 treatment, but with the way we look at quality of life. And
17 even though we have some pretty good ways of looking,
18 they're not good enough yet.

19 CHAIRMAN McGUIRE: And it has to do with
20 expectation.

21 DR. LEBWOHL: That's right.

22 CHAIRMAN McGUIRE: Rob ?

23 DR. STERN: I obviously think, since I've spent
24 some time thinking about quality of life and doing some work
25 in it, that it's an important area. I think at this point I

1 have some substantial concerns about using for this disease
2 quality-of-life outcome measures as an endpoint either for
3 approval or even for labeling. I think on the other hand
4 the agency can encourage companies that this is not from an
5 approval point of view but, clearly, this is something that
6 is out there in the public eye, out there from the
7 standpoint of the people who are now paying for drugs and
8 deciding whether to add another psoriasis drug to their
9 formulary, that I would hope one would encourage improvement
10 of this.

11 One of my greatest concerns is--and I notice we
12 had this package about conflict of interest--of all of the
13 areas where I think it's possible to game without dishonesty
14 outcomes, because it's in its infancy--and the former chief
15 of medicine at Georgetown who's now with the Federal
16 Government I think showed this very well, that one has to
17 be--that the chances of being able to game this through
18 design and analysis and have a favorable outcome are greater
19 than even in the relatively subjective/objective measures we
20 have been talking about.

21 So I think quality of life is something that needs
22 to be addressed. We need to learn a lot more. It needs to
23 be done in a more rigorous, less commercial way, but it
24 shouldn't be part of approval or package inserts at this
25 point .

1 CHAIRMAN MCGUIRE: Dr. Kilpatrick?

2 DR. KILPATRICK: Well, I want to come back to
3 quality of life in one sense and reflect my opinion of these
4 questions that they do not--they leave something out, which
5 I consider to be quite serious, and that is, in referring to
6 the two experts' presentations this morning, we heard about
7 the need for follow-up, the need for duration, and we
8 haven't talked about those at all.

9 Quality of life is not an instantaneous thing.
10 It's over some period. So I don't know whether, Jon, you
11 want to bring that into the approval process or the labeling
12 process, but I would like to hear some discussion about the
13 duration of therapy, of efficacious therapy, and follow-up.

14 DR. WILKIN: There are the other aspects, just
15 getting into one of the two successful categories, complete
16 clearing or near clearing. Should there be an additional
17 hurdle in terms of if they get to that stage, should they
18 have X number of weeks or months that they stay in
19 remission? And we would be very receptive to hearing from
20 the committee on that.

21 I would say we enjoy being able to put that into
22 the clinical studies section. If the sponsor has adequately
23 designed a trial in which they look at duration of
24 remission, we would want that information in.

25 But the question that should come back to the

1 committee is: One, is it a requirement that they would meet
2 a minimum remission period of--I forget what--I think you
3 had one you suggested. Or should it be a requirement that
4 they do the study and report it and it comes out in the
5 labeling?

6 Those might be your recommendations.

7 CHAIRMAN MCGUIRE: Dr. Wilkin, I think that you
8 and Dr. Kilpatrick may be talking about slightly different
9 issues. You're talking about durability of remission.
10 Quality of life is a more complex, much more global issue.
11 Do you want to talk about durability of remission?

12 DR. WILKIN: I thought he had indicated we were
13 now off the question list, so he has transcended Question
14 2.6 But, you know, if you are talking about quality of
15 life, I think that, even though we've heard some negative
16 things about quality of life, I think we would still be very
17 eager to hear from the sponsor, you know, how they might
18 want to look at quality of life and how they would propose
19 to assess it.

20 CHAIRMAN MCGUIRE: Dr. Drake had a comment.

21 DR. DRAKE: Well, you know, I've been doing a lot
22 of quality-of-life work, too, and that is thanks--or un-
23 thanks--to Dr. Wilkin, who got me into this about five years
24 ago, with nail disease. And, in fact, there is no question
25 that nail disease has a significant impact on quality of

1 life. It interferes with their social interactions, their
2 professional interactions, their employability. It
3 interferes with their function, and it interferes--I mean,
4 another factor of quality of life can be cost. All these
5 things impact.

6 We have done the kind of necessary work that you.
7 have to do for me to be able to say that. We've done the
8 validation of studies in the U.S. , plus we even did an
9 international study, and we did the international
10 harmonization and validation of the questionnaires.

11 You can use traditional instruments, such as the
12 SF form or the personal well-being form and collect basic
13 information. But when you get into disease-specific
14 questions, then you really need a validated instrument.

15 I can tell you that with respect to nail disease,
16 which psoriasis also impacts, it will impact your quality-
17 of-life score.

18 Now , I think psoriasis may even be worse about
19 affecting your quality of life because not only do you have
20 nail involvement, in many patients with psoriasis, which I
21 can say unequivocally has an impact on quality of life, I
22 think, Mark, you showed the picture of the guy with the
23 blood seeping through his white shirt. You can't tell me
24 what his quality of life--with a properly designed
25 instrument that pulls out the proper questions--I mean,

1 you've got to have ICC coefficients that are correct.
2 You've got to have alpha (?) box score, and you've got to
3 have all that stuff. You've got to have a validated
4 instrument . But once you do it, I'm absolutely convinced
5 you're going to find that psoriasis has significant impact
6 on quality of life. Now--the first part of the question.

7 B, should it be part of the mandatory requirement
8 for drug approval? I would say probably not at this point
9 because, in my opinion, we don't have the sophisticated
10 disease-specific instrument to that point yet. Plus I think
11 quality-of-life studies are really hard to do and do well.
12 And, frankly, the n-value that you've got to have, often the
13 power requirements of a study are such that if you add the
14 level of sophistication that's required for quality of life,
15 it might make the cost of doing the study prohibitive for
16 the sponsor.

17 So I would suggest that you may want to separate
18 out quality of life into separate components where, you
19 know, if somebody wants to do it, that would be fine. I
20 agree with Dr. Rosenberg's assessment, though. You can get
21 a lot of the--you "could use personal well-being scales with
22 these studies that are not actual quality of life, the total
23 instrument, but, you know, are standardized and would
24 provide useful information.

25 So I don't think you have to have quality-of-life

1 studies as part of the approval process because I'm afraid
2 it would preclude some companies maybe from getting into it
3 with good drugs. On the other hand, I think as a separate
4 issue, it should continue to be pursued.

5 CHAIRMAN McGUIRE: Dr. Simmons-O'Brien?

6 DR. SIMMONS-O'BRIEN: I agree with Dr. Drake. I
7 was just sitting here thinking that patient self-assessment,
8 almost like well-being during the study, I think would be
9 very helpful and useful information. Most of my patients
10 with psoriasis first--and maybe I'm just seeing a skewed
11 population, but they first want relief--

12 DR. DRAKE: Yes, they're miserable.

13 DR. SIMMONS-O'BRIEN: --from pain, burning,
14 itching, bleedings. Then they want to see it start to go
15 away. Then they want it ultimately gone or want it to stay
16 gone for a while. But they're usually in pain of some sort.
17 So I think that when a patient is in a trial, for that
18 patient to be able to grade somehow alleviation of symptoms
19 or how they're feeling better physically is helpful
20 information, because we have plenty of medications that we
21 use topically for other conditions that make patients worse
22 before they get better, even systemic treatments. And this
23 is not a population, I would think, that would tolerate
24 getting worse before they got better. However, I'm sure
25 there are some people who would be willing to get worse if

1 they knew that they were going to get better.

2 So I think it's helpful to have patient self-
3 assessment scores.

4 CHAIRMAN MCGUIRE: But you propose that those be
5 criteria for a study?

6 DR. SIMMONS-O'BRIEN : Well, I don't know. I thi:nk
7 it would be useful information, and I guess my only concern
8 would be if there is a topical agent down the road--and now
9 that we're getting into immunologic treatments, I think it
10 would be real important for patients to know who are going
11 to be using that medication, that they might, in fact, get
12 much worse before they start to see improvement.

13 CHAIRMAN MCGUIRE: So this could even--

14 DR. SIMMONS-O'BRIEN: Without us telling them--you
15 know, finding out on our own when we treat patients, oops,
16 out, yes, you will get better in a few weeks.

17 CHAIRMAN MCGUIRE: But that could happen post-
18 marketing.

19 DR. SIMMONS-O'BRIEN: Yes.

20 CHAIRMAN MCGUIRE: Dr. Wilkin?

21 DR. WILKIN: Well, I thought I heard in the
22 discussion, especially when Dr. Rosenberg earlier was
23 talking, about patient assessment. I had the idea that you
24 meant more just patient assessment of how their psoriasis
25 improved. I think there's a difference. And one is, how

1 has your life improved with this treatment? The other is,
2 how has your psoriasis improved? And we would be, you know,
3 happy to accept as a secondary endpoint, meaning something
4 that could be crafted into labeling, a well-structure
5 patient global at the end. I mean, it could be a visual
6 analog scale. It could be categorical, something like that.

7 DR. DRAKE: That's great. I'd recommend that. I
8 like that.

9 DR. WILKIN: But back onto the quality of life, we
10 re-read the paper in the British Journal of Dermatology, and
11 then shortly after that, Mark had a very nice editorial in
12 The Lancet where that was the focus. And I'll not steal
13 your thunder if you want to give the...

14 DR. LEBWOHL: Well, you know, I will say that they
15 used some pretty sophisticated and very well validated
16 studies. They did look at the psoriasis stress life
17 inventory, the psoriasis disability index. Treatments
18 weren't great at changing those.

19 Now, if we're not making it a requirement, the
20 value of having those studies is that--you know, Lynn
21 mentioned that patient I showed with the blood coming
22 through his shirt. The most useful piece of information, as
23 you look at each of these indices, is what the patients
24 write in their comments. And for every patient it ends up
25 being something different. One guy just wants to be able to

1 wear white shirts. Another patient wants to be able to get
2 undressed in front of his or her spouse without having to be
3 embarrassed about skin lesions. And you can't imagine the
4 range of different items.

5 I think you have to ask yourself: Why then don't
6 we have one that when we clear a patient with therapy, the
7 quality-of-life index that we're using shows that we're
8 improving that patient's quality of life? Because, so far,
9 every time it's been done--go look at the publications.
10 Hardly ever impacts in a positive way on the patient's
11 quality-of-life questionnaires that they fill out for us.

12 The value of having it is that we ought to be able
13 to have one that is better. If you made it a requirement,
14 you can be absolutely sure that the pharmaceutical industry
15 would scurry to make a better quality-of-life questionnaire
16 for us. But right now we don't have it.

17 CHAIRMAN MCGUIRE: Dr. Rosenberg?

18 DR. ROSENBERG: Another question. Or are we still
19 on this?

20 CHAIRMAN MCGUIRE: I think this question is pretty
21 much- -

22 DR. ROSENBERG: Another question. I think we
23 should consider capturing some information about joints,
24 whether they hurt. I don't want to get into--I'm not
25 qualified to do a rheumatological examination. I don't

1 check that bullet on the code. But I do ask how they feel,
2 and depending on the treatment, particularly the systemic
3 ones, this is important information. And I think we ought
4 to at least consider, while we sit here today, whether we
5 want to be asking for that on studies.

6 CHAIRMAN MCGUIRE: Well, I won't answer for the
7 agency because it's not appropriate. But if we begin
8 dealing with systemic immunotherapy, we will be asking lots
9 and lots of questions. I mean, that's going to be a very
10 complex tracking.

11 Mike, do you or Jon want to respond to that?

12 [No response.]

13 CHAIRMAN MCGUIRE: I'm a little concerned that
14 we've talked about duration of remission, but we've sort of
15 let--it's sort of been lost. Is the agency interested in
16 that?

17 DR. WILKIN: I think we would be very keen to, at
18 a minimum, craft it into the labeling. The question that
19 the committee could take up is whether it should be a
20 requirement to follow patients out a minimum period of time
21 to find out what that might be. You could recommend that or
22 that could be optional. It could be an incentive that if a
23 sponsor thought they had a medication that would provide for
24 a substantial remission, then it would show up in the
25 clinical studies section.

1 CHAIRMAN MCGUIRE: Well, I don't think any of us
2 wants to do anything that's not good medical practice, and.
3 what we do at a practical level is treat until there is a
4 near remission or a remission and then reduce treatment and
5 reduce treatment and see when disease recurs.

6 That's hard to do in a very formal way, to make
7 stringent recommendations for a sponsor to do that, because
8 you're doing something that's not--I wouldn't be comfortable
9 with medic--but I'd be happy to hear what other people have
10 to say about it.

11 DR. KO: Mr. Chairman?

12 CHAIRMAN MCGUIRE: Dr. Ko?

13 DR. KO: I can make a comment on this because I
14 have seen some applications where they looked at this.

15 One problem in this kind of data is that the
16 studies do not have the good placebo arm to compare,
17 because, as you know, remission rarely occurs with the
18 placebo arm. So they are really having the treatment,
19 active treatment arm giving a certain duration with the data
20 on time to relapse after cessation of therapy. They need to
21 follow them up for a certain period of time. But it is very
22 hard to interpret that kind of data because the disease
23 itself may fluctuate in intensity.

24 so, really, even if you get the data, it is hard
25 to interpret.

1 CHAIRMAN McGUIRE: Dr. Wilkin?

2 DR. WILKIN: Yes, and the comment, actually, Joe,
3 that you made just before that, I think you were getting
4 into the notion that in Phase III we are really not
5 replicating what happens in the dermatologist's clinic.
6 What we're really trying to do is we're trying to tease out
7 the effect of the active. That's the goal. The
8 dermatologist is more successful than the percentage that
9 would emerge from a Phase III study, because you seldom do
10 one thing. You will be talking to people about the soaps
11 they use and emollients and these sorts of things, and often
12 that is not part of a Phase III trial.

13 CHAIRMAN McGUIRE: Yes, Rob ?

14 DR. STERN: I think Dr. Ko's point is an excellent
15 one in terms of time-to-flare studies have to be randomized
16 or they're meaningless. However, I think if you look at the
17 cup as three-quarters empty, I think there is some
18 information that one can obtain from follow-up of people who
19 have said to have reached whatever this magic level is, that
20 if it's not durable for some minimum period of time, it sure
21 as heck is--in patients with stable plaque-type psoriasis,
22 it's sure not very impressive. So as opposed to trying to
23 get to say some positive statement that compared to people
24 induced with other agents or who used other things, this did
25 better or worse long term, a statement of the proportion of

1 people who bounced back within a relatively short period may
2 have some important information for the clinician about
3 either how the drug needs to be used or whether this is
4 anything really dynamite. And that's much more amenable to
5 analysis.

6 So if you tell me within 30 days of stopping
7 treatment 80 percent of people had reoccurrence of their
8 patches, I would say so it works, but you got to keep on
9 using it forever, I guess. And that's an important clinical
10 piece of information.

11 CHAIRMAN McGUIRE: Dr. Rosenberg?

12 DR. ROSENBERG: We used to treat acne on and on,
13 you know, and then Acutane came out and that's the thing
14 with Acutane. You take it, and for a high percentage of
15 patients, they don't have to take--there's no more need to
16 treat their acne. And I think we are talking about
17 medicines that are going to be high-powered, some of them,
18 and very good, we hope. And if we can get an Acutane, why,
19 it would be nice to know it, although I guess when that
20 happens we could soon find it out and get that information.

21 CHAIRMAN McGUIRE: Dr. Lim?

22 DR. LIM: I think it's also a piece of information
23 that is important to have. I don't think that should be the
24 one that is needed for approval, but I think it is a piece
25 of information that is important for us to have and also for

1 practicing dermatologists to know about.

2 The next step, then, you know, what we have to
3 define and what is considered to be recurrence, and how many
4 percent of the original lesion would have to come back, I
5 think that would be another aspect that has to be
6 considered. But I think it is another piece of information
7 that is good to have.

8 DR. ROSENBERG: You know, if Acutane only lasted
9 for two and a half months, nobody would want it either. If
10 we just stopped the Acutane study the day they finished the
11 treatment and didn't know that it was all going to come
12 back, there would be no point in having Acutane. So I think
13 the approval of Acutane is based on the fact that it's a
14 jolt, but then you get a long ride from it. Enough of that.

15 CHAIRMAN MCGUIRE: Dr. Weintraub and Dr. Wilkin,
16 have we answered your questions?

17 DR. MARZELLA: I wanted to ask a question about--

18 CHAIRMAN MCGUIRE: Dr. Marzella?

19 DR. MARZELLA: Thank you. I wanted to ask a
20 question about entry criteria. Sometimes in designing a
21 particular clinical trial, because of risk/benefit
22 considerations, it may be important to allow for entry of
23 only patients that have moderately severe or severe
24 psoriasis. And I was wondering if the committee could
25 provide some guidance about what criteria could be used to

1 define those subsets of patients.

2 CHAIRMAN McGUIRE: I thought things were winding
3 down.

4 [Laughter.]

5 DR. ROSENBERG: I think it should be like Acutane.
6 You shouldn't take Acutane unless you have severe disease,
7 with modulo-cystic disease, scarring that could not be
8 controlled with tetracycline or other antibiotics. That's
9 reasonable. And I think comparable statements can be drawn
10 for psoriasis in terms of the description of it and its
11 failure to be controlled with more standard, known to be
12 safe, reasonable agents.

13 CHAIRMAN McGUIRE: I think we're about finished.
14 Let me bring up a few items. First, Jon and Mark and Rob,
15 thanks very much for giving us your day. It's been
16 extremely valuable. We couldn't have gotten through it
17 without you.

18 Seymour is on his feet. What have you to tell us?

19 DR. RAND: Am I allowed to make a comment?

20 CHAIRMAN McGUIRE: Yes, you may.

21 DR. RAND: Okay. My name is Seymour Rand. I'm a
22 dermatologist from Arlington, Virginia, and I have been
23 involved in the drug regulatory and also drug development
24 business for several years.

25 I did want to ask--

1 CHAIRMAN MCGUIRE: Are you here for a sponsor or
2 just to speak for yourself?

3 DR. RAND: I'm here by myself, and there is no
4 conflict of interest.

5 I wanted to ask a general type question, which was
6 addressed earlier on the clear or almost clear treatment
7 success criteria, because I, too, was involved in the
8 onychomycosis guidelines a few years ago, and certainly I
9 understand when you have a primary infection, you certainly
10 do want to have a clear or almost clear condition, as well
11 as eradication of the organism.

12 However, in dermatology--and I am a practicing
13 dermatologist--most of the conditions we treat for which
14 drugs are available are inflammatory diseases for which a
15 clear or almost clear outcome is not usually possible.

16 Now, having worked at the FDA, I, you know,
17 respect the guidelines and respect the agency as well as the
18 division, and I just am asking the question now from the
19 viewpoint of a practicing dermatologist who would like to
20 see drugs get approved and made available to the practicing
21 dermatologist.

22 Recently, in the past year, the agency has
23 approved two drugs for male pattern androgenic alopecia, and
24 those approvals were not based on the clear or almost clear
25 condition, which would be the equivalent of growing all your

1 hair back or almost growing all your hair back, but, rather,
2 they were approved with increases in hair counts of only 15
3 percent over baseline as well as the majority of patients
4 only getting a mild improvement in their condition.

5 So the question I just pose, if you think it
6 should be discussed further, is: Are we being consistent as
7 physicians and drug development people to expect for
8 psoriasis, which is a much more severe disease, I think,
9 than male pattern androgenic alopecia, is it fair to expect
10 to get a clear or **almost clear** result?

11 **Then I would like to say this:** When I was a
12 **presenter at the onychomycosis** meeting four years ago, we
13 did take a vote on the questions that we asked the panel of
14 Advisory Committee members. And I'm just wondering if that
15 would be considered here, too, for a vote on the clear,
16 almost clear question that has been posed in, I think,
17 **Question 2.1.**

18 Those are my comments, and thank you for your
19 time.

20 **CHAIRMAN MCGUIRE:** Thank you. Those are important
21 points. I think Dr. Wilkin has emphasized the difference
22 between this kind of a study and an onychomycosis study.
23 And it was my feeling that we had discussed the value of
24 clear and the difficulty of achieving clear in psoriasis,
25 and we had to look for an endpoint that was short of clear.

1 We were looking at something like 75 percent.

2 Comparing this with--I really don't want to get
3 into a polemic comparing this with Propecia or Rogaine.
4 There were a number of different issues involved, I think,
5 with male pattern baldness. Would anyone **from the agency**
6 like to respond to that? Mike, would you like to **say**
7 anything?

8 DR. WEINTRAUB: I wanted to thank Dr. Rand for
9 bringing up those issues, and it brings up a variety of
10 things I'd like to discuss.

11 First of all, we're a little earlier in this
12 process than perhaps we were in the onychomycosis process.
13 So that's the first thing. Yet if we do create a guidance--
14 and I hope we do--it will have to be written in the Federal
15 Register, presented again to this committee for comment, for
16 help, in case we went wrong.

17 The second thing is that we are also--so I
18 wouldn't worry about it, Seymour. You'll have plenty of
19 chances to discuss this.

20 And then, two, when we publish a guidance, it
21 really is a guidance. The industry doesn't have to pay--it
22 doesn't have to do it the way we tell them to. Neither we
23 nor the industry is really bound by a guidance, and that's
24 another very important thing to realize.

25 So by the time we get to a guidance, I hope it

1 will be refined. We'll have thought through all these
2 issues that were presented here today. I know it's been
3 very valuable for me, and there will be a chance for the
4 wider community to comment on it, and then a guidance is a
5 guidance.

6 CHAIRMAN MCGUIRE: Thank you, Michael.

7 We have something that is not spelled out very
8 well in your agenda, and if the consultants want to remain,
9 we'd love to have you. If you want to catch a plane, catch
10 a plane.

11 John Treaty, who is the Director of the Advisors
12 and Consultants Staff, is going to give you a brief overview
13 of the agency from the standpoint of how we interact with
14 the agency, certain issues about the FDA Modernization Act,
15 where PDUFA is and where we are with conflict of interest.

16 MR. TREACY: Joe, thank you for the introduction.
17 My name is John Treaty. I'm with the Advisors and
18 consultants Staff. I've got my phone number up here, and if
19 anything else in the rest of this meeting, there's one
20 message I have, and that message is call me.

21 We're going to cover a lot of things, and it's
22 just impossible for anyone to remember all of the nuances
23 that are involved. But, please, call me anytime. Call me
24 at home. Call me anyplace. It doesn't matter.

25 This next slide serves two purposes: one, this is

1 what my job description is **sometimes as a result of**
2 **meetings. It's also what Joe said was going to happen to me**
3 **if I went too long today on it.**

4 I was going to stop here because Joe asked me to
5 cover a couple of issues that I don't have slides for, and
6 they're real important. The first is dealing with the
7 press. I know I've dealt with the press a number of times,
8 I was just wondering how many of our members have dealt with
9 the press on their Advisory Committee.

10 [A show of hands.]

11 MR. TREACY: Joe and a few others. Great .

12 Let me just go over that a little bit. First and
13 foremost, the press is really important in our country.
14 [t's real important to FDA. We have a Press Office that
15 helps us get out information we need to get out. So I don't
16 want to discourage any interactions with the press.

17 But having said that, I need to give you your
18 options that you have, and you've got many options. One of
19 them is not to deal with the press at all, refer them all to
20 Joe or to the Executive Secretary or to me or to Mike or
21 Jon. That's clearly one of your options.

22 If you do choose to deal with the press, I have a
23 couple of suggestions only. This is a free country, so
24 you're free to deal with the press any way you'd like. One
25 is we really prefer that you not talk to the press before

1 meetings. They're going to come to you perhaps and ask you
2 about what's going to happen, and we really prefer that you
3 wait until you come to the meeting, hear all of the
4 evidence, hear what your co-members have to say before you
5 really go on record of what you think. So that's one thing
6 that I would advise you strongly.

7 Second, if you are going to deal with the press
8 back at your primary job, I do have a suggestion. One, if
9 they're going to talk to you, I would say ask them first to
10 fax over what kind of questions they're going to ask you,
11 take time to read them, and then call them back. This gives
12 you a chance. You're caught off guard when they call you.
13 You're dealing with patients. You're worried about other
14 things, and they catch you off guard. If you get them to
15 send you the questions, you get a chance to look at them,
16 look them over, feel comfortable with them. You get to sit
17 down and call them back on your terms. It really helps out
18 tremendously. So those are two strong hints I have for you
19 dealing with the press. One is don't do it beforehand, and,
20 No, take advantage of getting the questions and thinking
21 about them before you speak. And, of course, we have a
22 Press Office. If the press needs information on something,
23 they'll arrange to talk to Joe or Mike or Jon, or whatever.
24 So there's really no need, and you feel free. So this is a
25 service we do for you. Whatever you'd like to do in that

1 area, you're welcome to.

2 The second thing not on the slides that Joe wanted
3 me to talk about had to do with protection of confidential
4 information. Sometimes you will get background information
5 worth tens of millions of dollars. Particularly with small,
6 start-up corporations, the value of their stock can change
7 overnight tremendously, and we've had that happen. And a
8 lot has to do with the basis of their clinical trials. So
9 you're looking at simple information and the results of the
10 clinical trial. To people on Wall Street, that can be worth
11 tens of millions of dollars, particularly if the trial shows
12 it's a breakthrough drug or if the trial shows that it
13 doesn't work at all. Lots of times that's very important.

14 And getting back to the press part, sometimes
15 you'll get calls from folks who say they're from the press
16 or they're with such-and-such newsletter, and it turns out
17 what it is, it's a stock brokerage firm, and his newsletter
18 goes to the other stock brokers at the particular
19 institution. So you'll get calls beforehand. Be
20 particularly careful then when you're dealing with folks.

21 Also, you should have a locking file cabinet to
22 store these things in, and we will buy you one if you don't
23 have it. One of the few nice things we do for you. And, of
24 course, I guess I don't have to tell you about--well, maybe
25 do. The broken record technique which I find very useful.

1 For those of us old enough to remember when they had records
2 and the records would break and they'd repeat, when people
3 are grilling you, do you have any information on such-and-
4 such, you give the broken record answer: I can't divulge
5 that. I can't divulge that. I can't divulge that. So I
6 really recommend the broken record technique when you deal
7 with folks, for your brothers-in-law and all those other
8 folks who are pestering you for the different information.

9 Okay. Any questions about dealing with the press
10 or protecting confidential information, anything along those
11 lines? Great.

12 So I'll get back to my main job then, and the main
13 message, if I can remind you again, is call me if you have
14 any questions whatsoever with what we do.

15 I wasn't sure--I wanted to just touch base a
16 little bit about the big picture, how you interact with FDA.
17 I don't have an organization chart, but if I did, FDA would
18 be at the top and there would be six centers underneath it.
19 We're human drugs, and, of course, we're the biggest--and
20 the best--of all six centers. The others have to do with
21 foods, veterinary medicines, devices, toxicology, which was
22 in Little Rock, Arkansas, before our President was elected,
23 and our Center for Biologic Research and Evaluation, our
24 closest sister. They look at vaccines and drug products and
25 other issues.

1 CDER is about the size of two medium-size medical.
2 schools. We have about 1,700 employees; roughly about 200
3 of them are MDs, and last I checked, about 55 to 60 percent:
4 were MDs or PhDs. So we really do already have a lot of
5 scientists, but we still need your input. And we now have
6 18 advisory committees.

7 Within where I am--you've heard this--Advisors and
8 Consultants, we're independent from Mike and Jon to help
9 protect your independence, and we report direction to deputy
10 center director, and you don't need to know all that stuff.

11 A key question is: Why do we spend all this time
12 and effort on Advisory Committees? Gee, with all those MDs
13 and all those scientists, don't we have enough already?
14 Well, we don't really--we think we can do it, but it's much
15 better with Advisory Committees. We need to supplement, to
16 complement, to augment our internal scientific expertise.
17 But you really add a lot of credibility to our decisions.
18 The fact that we go out with a decision on a drug, the
19 academic community, the medical community, they know that we
20 have already taken this decision to a group of outsiders
21 such as yourself, and it just adds more credibility to what,
22 we do.

23 It also serves another purpose, which is to open
24 up our decision-making processes to the public. Most of the
25 time we're a black box behind doors. These are one of the

1 few occasions they can see what we're thinking about, what's
2 acceptable, what's going on. It really serves a very
3 important function, and also getting public input. I think
4 going back to the Thalidomide **meeting, you can think about**
5 the important public input we **got on that meeting. So these**
6 meetings serve a tremendously **important function.**

7 I put this chart up **here--and PDUFA, that's the**
8 bureaucratic word for the Prescription Drug User Fee Act
9 that started five years ago, and it's just been renewed.
10 And if you follow the papers, we've just done a tremendous
11 job, if I do say so myself, in speeding up drug approvals
12 and everything else.

13 DR. WEINTRAUB: I wonder if you could move a
14 little bit to your left.

15 MR. TREACY: Okay.

16 DR. WEINTRAUB: My left.

17 MR. TREACY: My right, okay.

18 DR. KILPATRICK: I'm wondering, could you move a
19 little bit to the right?

20 [Laughter.]

21 MR. TREACY: Is this all right? Okay.

22 PDUFA is the bureaucratic--but you can see, with
23 the start of PDUFA that's when we went from 32 meetings a
24 **year** to 50 a year, and we continue to do them. And one of
25 the reasons, we think it really helps speed up the process.

1 And I can see how putting together a group of smart
2 individuals from the outside along with the internal experts
3 at FDA, along with the sponsor, and having your time for a
4 full day really helps make the decision much faster.

5 PDUFA has some strict time frames, and one of the
6 things you're probably aware of is it's led to a lot of
7 scheduling problems, and you can see we now schedule and
8 cancel as **many** meetings as we hold. So we really ask your
9 forbearance on this. A lot of these meetings are scheduled.
10 The sponsor is not ready or something happens, and we have
11 to go ahead and cancel that.

12 I was going to talk a little bit about conflict of
13 interest, too. This is really important. In your handouts--
14 --I don't have a slide of it--there's an article that was in
15 the Wall Street Journal, and it's based on an article I
16 assume you've already read in the New England Journal of
17 Medicine about the possibility of bias reaching into
18 research. So that's an important reason that we do look at
19 conflict of interest. That article received a lot of
20 attention.

21 I don't know how you can define conflict of
22 interest. It could be anything to anyone. But we've got
23 four people who've told us what conflict of interest is.
24 One is Congress, in the law what they said it is. The
25 President, having seen what Congress said, made some

1 changes, added a few things to it. The recent FDA
2 Modernization Act adds another part to conflict of interest,
3 and then we at FDA go ahead on our own, add some more
4 aspects of conflict of interest, which I'll touch on really
5 quickly.

6 I'm going to, as I said, move fairly quickly here.

7 Congress defined conflict of interest as applying
8 to you, your spouse, your minor children, your employer,
9 organizations you serve as director, and other things. So
10 it covers a lot, particularly the word "your employer. "
11 Most of you work at large research institutes, and,
12 unfortunately, their financial interest are imputed to you,
13 and that causes a lot of work.

14 There's no dollar threshold involved, so if it's
15 \$1 or \$10 million, it still counts.

16 There's also some limitations on it. It only
17 applies to current financial interests, so the day that your
18 grant ends, your financial interest ends, according to
19 Congress.

20 DR. MILLER: What's 18 U.S.C. 208?

21 MR. TREACY: Oh, that's the U.S. Code of
22 Regulations, which actually is where the law is printed. so
23 if you look at 18 U.S.C. Section 208, it gives you what the
24 conflict of interest laws are.

25 The President--I think it was President Nixon,

n 1 actually, at the time--when he saw that, he made some
2 additional requirements, and these aren't by law. These are
3 by administrative order. And what they did is he talked
4 about besides avoiding what Congress said, you've got to
5 avoid this because the President has told you you need to do
6 it. So he expanded it to talk about appearance of
7 impartiality.

8 For example, where previously the Congress said if
9 you're negotiating employment, that counts as if you have a
10 financial interest in the company. The President's
11 Executive Order said, gee, if you're also negotiating a
12 contract with someone, you've got to avoid that appearance
13 of conflict.

14 MS. RILEY : I think that may be a contradictory
15 statement. I think you want to avoid the appearance of
16 partiality.

17 MR. TREACY : Yes. Thank you very much, Tracy. I
18 was going to irregardless of what I had done. But the
19 appearance of partiality is what we--thanks. And it
20 extended--for example, I said that your financial interest
21 when your grant or contract ended. The Presidential
22 Executive Order extends it out to one year afterwards. So
23 you have certain limitations on it.

24 The most recent FDA Modernization Act that just
25 went into effect February 19th applies only to voting, and

1 it says you can't be granted a waiver if you're going to
2 review your own work.

3 I'll just move on a little bit here in terms of
4 FDA policies, what we do. We extend conflict of interest to
5 all our guests who come here who may not be Federal
6 employees and consultants because we think that's important.
7 We ask the public who come and speak to disclose their
8 financial interests, and we have always had this rule about
9 you can't review one's own work that Congress just codified.

10 As you figured out, we spend a lot of time on
11 conflict of interest, and I hope this sets the context. It
12 really is a dilemma. We seek out the best scientists, those
13 that work at large research institutes, who are active
14 researchers, and obviously you're the folks that most likely
15 **nave** conflicts. And the normal government solutions that
16 **apply** to me and Jon and Mike don't apply to you. We can't
17 **tell** you to quit your other job to come to work for us two
18 **days** a year. Or we can't say, hey, that's great, just never
19 **work** for us on these issues. It just doesn't work. And
20 **Congress** recognized that, and they added a provision under
21 **208**, which you now know is the U.S. Code, that allows us to
22 grant waivers. When we feel that the need for you to serve
23 on the committee outweighs that appearance of conflict of
24 interest or the conflict of interest, we can go ahead and
25 **grant** you waivers. So we spend a lot of time on that.

1 The Office of Government Ethics, which is the part
2 of the U.S. Government that oversees ethics, just passed
3 some regulations that make it a little bit easier for us to
4 deal with this. They recognized the robustness of the
5 Advisory Committee system in their regulations. They use a
6 lot of FDA Advisory Committee examples in their regulations
7 that they have granted. And they have gone ahead and
8 granted these broad exemptions to all Federal Government
9 Advisory Committee members for whenever you deal with a
10 matter of broad applicability, having to deal with basically
11 guidelines for drug development. And their example they use
12 is an FDA Committee where we could be allowed to have
13 actually members from industry, employed by industry serving
14 our committees when they did deal with those issues.

15 I'm going to move on to another related issue.
16 Any questions about conflict of interest? I tried to skim
17 over it really fast, remembering the number one thing is to
18 call me if you have any questions on it.

19 Another issue that comes up from time to time, you
20 folks are active researchers developing drugs on your own or
21 through your universities, and often you may be asked by a
22 sponsor to represent them at a meeting before FDA, before
23 this Advisory Committee, something that we wouldn't allow.
24 But the answer is you may or may not be allowed to represent
25 that sponsor, and we have a written document that lays out

1 our policy on it. It's called the MAPP, and it's the last
2 four pages of your handout. Key to it, you should really
3 let us know when you're asked to do it by a sponsor, and we
4 can get you an answer whether you will be allowed to do it..

5 Some representational activities are just illegal;
6 you can't do them. If you've ever worked for us on a
7 particular application, you can never work--you have a
8 lifetime ban on representing someone else.

9 Other cases, we just wouldn't allow it. We
10 wouldn't allow you to represent a sponsor before your own
11 committee. We'd just say you can't do it.

12 But there might be occasions, if you were the
13 principal investigator in development of the drug and you
14 had a meeting in the Review Division, we might consider
15 that, especially if it's in a different division than the
16 one associated with this committee.

17 DR. DiGIOVANNA: Could you maybe just define for
18 me representation? By representation, you mean not being an
19 investigation on a study but actually either presenting--

20 CHAIRMAN MCGUIRE: John, I don't think anybody can
21 hear you. See if your mike is one.

22 DR. DiGIOVANNA: I asked for an expansion or
23 definition of what representation means. Does it mean
24 physically representing or in word or deed representing? Or
25 does it also include issues such as being investigators on--

1 MR. TREACY: It's a very narrow definition. It's
2 actually being with the sponsor talking to FDA about the
3 application. You can do all the work behind the scenes that
4 you want. That's not a problem. But you can't be there.
5 And there is a slight expansion of some case law. The fact
6 that you don't say anything doesn't matter. As long **as you**
7 **come** in and are sitting with the sponsor, you can't whisper
8 something to him to speak to FDA, So that's a good point.
9 You can continue to do **all your research**. It's just that
10 you won't be able to present it to the committee or perhaps
11 not be able to present it to the Review Division. And
12 that's typically by law, or the one dealing with the
13 committee. We just think it's too strong a conflict to
14 actually have you sitting here one day and the next day
15 representing a sponsor. It's something we wouldn't allow.

16 DR. LIM: What if you are a member of, say, a data
17 endpoint review committee for a study that the sponsor is
18 doing, and then that particular product and the sponsor come
19 up to the committee? Should you excuse yourself from
20 reviewing that particular application?

21 MR. TREACY: Possibly. This would say you can't
22 be there with the sponsor to give the information. Many of
23 our folks are on data boards, and probably you would be
24 excluded. But there may be circumstances--we have this
25 capability to weigh the need for you versus the conflict of

1 interest. So I can't give you a specific answer on that,
2 but you definitely would not be able to represent the
3 sponsor before FDA.

4 Any other questions about that? Okay.

5 I see I skipped a couple charts. This gives the
6 context of why we meet the way we meet here. In 1972, for
7 those folks who may remember Watergate, this is 1972 when
8 there was a lot of concern about closed-door government, and
9 they passed the Federal Advisory **Committee Act that really**
10 opened up our ability to deal with outside experts. Things
11 were no longer made behind closed doors. It required things
12 such as advance notice. We've got to publish at least 15
13 days in advance that these meetings are coming. They've got
14 to be open to the public. We have to allow media coverage.
15 There's got to be opportunity for public participation. We
16 set aside one hour at every meeting, at least, for folks who
17 would like to come and speak.

18 There's a requirement for fair balance in terms of
19 membership on the **committee. We handle it by trying to have**
20 **the right balance of folks on it. We have a statistician, a**
21 **consumer representative, as well as our ophthalmologists and**
22 **our dermatologists. And it's really important that we have**
23 **all side presented to you.**

24 Now, a key part of what goes on is your
25 independence, and this is really critical to us. Never give

1 us the answer you think we'd like to have. You're not doing
2 us a service. The way we help try to give you your
3 independence to tell us exactly what you feel is that you're
4 selected by the commissioner based typically on the
5 recommendation of the Review Division, but you're here for a
6 fixed term. I know Joel was saying do we ever rate the
7 members here to see how they're doing. The answer is we
8 don't. Part of it is the only way you can really get kicked
9 off the committee is if you don't show up for a few years or
10 you do something truly outrageous.

11 But you're here. We have to put up with you no
12 matter what you say for the terms you're on, either three or
13 four years, or whatever. So that's one way we guarantee
14 your independence .

15 You're supposed to receive material input from all
16 sides. You get a sponsor package, get a package from FDA.
17 You can listen to the public. You get all inputs from all
18 sides, and that tries to do this.

19 There's a large role played by the Chair by
20 regulation. Once we start, the Chair gets to run the
21 meeting. Mike or Jon or myself, we can't tell him what to
22 do. I think once--he's got to allow to have that one hour
23 of public hearing, but otherwise, he's allowed to run the
24 meeting as he sees fit, and there's nothing we can do to
25 stop him, basically. That's another part of this committee

1 independence.

2 We spend a lot of time on conflict of interest and
3 bias, but that really adds a lot of credibility. I know
4 it's a lot of work on your part, but having a committee
5 **that's been screened for** conflict of interest really adds
6 **more credibility to what** you folks are doing.

7 **So those are a** little bit--I promised to finish
8 **quickly, and I'll finish,** again, with my job description.
9 And I would say I want it to be my job description, not
10 necessarily your job description. So anytime you have any
11 question, please let us know, particularly about a conflict
12 of interest or other stuff.

13 I will say you make very **important decisions that**
14 night involve--I mentioned earlier money. Some of our
15 **decisions** do involve tens and hundreds of millions of
16 **dollars.** If a company is unhappy with what happened, they
17 **will go to great lengths** to try to undermine the credibility
18 of the decision of the committee, and one of the things they
19 look at frequently is conflict of interest. So,
20 **unfortunately,** I think it's one of the bigger complaints I
21 **get** from you folks, but it's something that we have to deal
22 **with** all the time.

23 I guess I don't have to ask you--the most
24 important thing about my presentation today is call me if
25 you have any questions about anything.

1 With that, if there are any questions, I'll be
2 ready to go.

3 CHAIRMAN MCGUIRE: We can have questions from the
4 Advisory Committee. John, I appreciate you taking the time
5 to come over, and I know that you have put together a day-
6 and-a-half training session for Advisory Committee members.

7 MR. TREACY: Yes, sure.

8 CHAIRMAN MCGUIRE: It's my understanding that that
9 is going to be a requirement for new appointments.

10 MR. TREACY: Right. The new legislation includes
11 a requirement that we train all our Advisory Committee
12 members. Twice a year we have a day-and-a-half training set
13 aside. We have some background material we should be
14 sending you. It's a great opportunity for one-on-one
15 interactions. Our Chair can help train you and with Tracy,
16 our Executive Secretaries. Any questions you have we'll be
17 happy to help you.

18 Henry?

19 DR. LIM: On that one day and a half, if one has
20 been trained previously at another Federal branch on
21 conflict of interest, do we still have to attend the day and
22 a half?

23 MR. TREACY: The day-and-a-half training, only
24 part of it is on conflict of interest. A lot has to do--a
25 half-day is spent in the Review Division. You get an

1 overview. We have typically Mike Friedman comes down,
2 someone from our Consumer Affairs Office comes down. We've
3 got a lot of folks to come to listen to what you have to say
4 as well as tell you what we're looking for, what standards
5 we use in the approval of drugs. So it focuses mainly on
6 other things besides conflict of interest.

7 But I would encourage everyone to come. Joe, I
8 know you have attended two of our sessions, I think one for
9 the members and one for our Chairs. We also have an annual
10 training session for our Chairs. One would think they
11 didn't need it, but they actually turn out to be some of our
12 best sessions. We learn more from the Chairs, I think, than
13 they learn from us.

14 CHAIRMAN McGUIRE: That is a remedial session.

15 [Laughter.]

16 DR. KILPATRICK: I have to ask a question. Dr.
17 McGuire, did you pass that examination?

18 [Laughter.]

19 CHAIRMAN McGUIRE: Yes. You just had to be there.

20 MR. TREACY: As I said, we've checked into this,
21 by the way, several times. It is not possible to fire Joe.
22 We've looked at it.

23 [Laughter.]

24 CHAIRMAN McGUIRE: There were two other things I
25 wanted to mention. One is that at the Council of Chairs,

1 one of the vice presidents for R&D at Procter & Gamble
2 spoke, and I intended to send every member copies of his
3 overheads, and I hope you got them.

4 The sponsors take this event very, very seriously.
5 They prepare for it. It is financially extremely important
6 for them. And they want to know that we take the process
7 seriously. It hurts them to believe that we did all of our
8 homework on the plane flying in. They rehearse, and they
9 rehearse with people representing John DiGiovanna. I don't
10 know where they find them, but they have somebody who would
11 answer questions the way that John answers questions or asks
12 questions the way John does. They have some person, I
13 guess, who is a McGuire and who asks questions that are my
14 kind of questions. And they go through this and they
15 rehearse and rehearse and rehearse.

16 When you sit at one of these meetings and you said
17 I have a question about such-and-such and the presenter says
18 Carousel 3, No. 32, that means that that question has
19 already been asked at their rehearsal. And so they do not
20 want one of us to dominate the meeting. They don't want the
21 Chair to dominate the meeting. They want equal
22 participation. They hate to be scheduled in the afternoon
23 because they know that people start peeling off in the
24 afternoon to catch flights to the coast.

25 If you didn't look at those overheads, and if you

1 haven't thrown them away, take a look at them, because that
2 really was the best expression of what industry's interest
3 are. And he was quite, quite clear on those points.

4 Another point came up in the Modernization Act
5 that John didn't have time to cover, but in the language,
6 there will be disease advocates, disease representatives,
7 and there will also be representatives from industry. And
8 it was not clear from the language whether those people
9 would have votes on the committee or not. And it's looking
10 like industry does not want to have a vote on the committee,
11 and, in fact, industry is not quite sure that they got what
12 they politicked for. But the language is there. So I
13 assume we'll start seeing representatives from industry on
14 this committee.

15 There is also an FDA home page, and you can log
16 into that, and you can get the--my office is so chaotic that
17 whenever I call John, I go to the home page and look up his
18 number. You know, I reinvent it every time. But it's easy
19 to do, and they are putting more and more information on the
20 home page.

21 What John has promised us is that there will be--
22 they will work out some sort of access, privileged access,
23 and each of us will have codes to log on and to get
24 information about drugs that are being moved through the
25 process. And that sounds easy. It's complicated, but--

1 MR. TREACY: Right. It's going to involve perhaps
2 encryption software that you will have to have, and we will
3 have to have on our system or arranging for a dial-up for
4 you. And we're trying to work out the details of that.

5 Right now any mail you send via e-mail is not
6 protected information, so we can't just do it simply by
7 e-mail.

8 CHAIRMAN McGUIRE: Questions?

9 DR. MINDEL: Could we, as a perk, be offered a
10 copy of the transcript of the meetings that we participate
11 in?

12 MR. TREACY: Yes. As a **matter of** fact, they will.
13 be on our home page. Right now many of our transcripts are
14 on, and as soon as we get permission to put our home page
15 up, we will have all of the transcripts since, I think, 1996
16 when we started to get them electronically in some form. so
17 if you'd like a transcript, we'll be happy to send it to
18 you. Or shortly you'll be able to get it right off the home
19 page.

20 Separately, we are also--one of the frequently
21 requested FOI documents are your CVs by these companies who
22 are getting ready for meetings. So I think we've sent out
23 asking you if you'd like--we have one on record, but we've
24 asked you if you'd like to send a replacement in. That will
25 probably also be put on the home page soon. So those are

1 some of the frequently requested information.

2 DR. DRAKE: What if we don't want our CV on the
3 home page? Can we decline if we're a member of this
4 committee?

5 MR. TREACY: No. Unfortunately, if you give us a
6 CV that you'd like us to put on, we can, but you don't have
7 an option on this. Just as my CV is available under Freedom
8 of Information, that's just part of the government record.
9 When you agree to serve on the committee, unfortunately,
10 that was one of the requirements, that a CV be available for
11 you. So if you have a CV that you'd like us to put on in
12 place of your current one, we will go ahead and eliminate
13 things such as your Social Security number and children and
14 personal things like that. But we've given everyone the
15 opportunity if you'd like us to put on a briefer one, we'll.
16 be happy to do that for you.

17 CHAIRMAN MCGUIRE: John, thanks again for your
18 time.

19 Oh, Fred?

20 DR. MILLER: Joe, when is the next training
21 meeting? Is that coming up?

22 MR. TREACY: May 14th and 15th, and the next one
23 after that is in July. July 16th.

24 DR. DRAKE: Is that required, did you say, for all
25 of us or new members or--

1 MR. TREACY: Well, the current--

2 DR. DRAKE: I obviously would like to come, but
3 I'm just trying to figure out if we can.

4 MR. TREACY: What the law says now is we have to
5 train you. Now, it doesn't say what--today you could
6 consider a training session, if you so chose to do it. But
7 we have set in place--we have a video that will soon be
8 coming out in which some of you--I'm not sure if anyone from
9 this committee is on it. They'll be going out. We have a
10 guide for members. And we do hold these periodic training
11 sessions available for folks. So the law is moot on it.

12 CHAIRMAN MCGUIRE: I'd forgotten about that. They
13 have a video of a meeting of us--fortunately, not us
14 precisely, but us. And there are people yawning and
15 scratching and picking and rolling around on the floor, and
16 it's a great training film.

17 [Laughter.]

18 CHAIRMAN MCGUIRE: You only have to see it once.

19 DR. MILLER: One and a half days, that's in
20 addition to any films or anything that we might see; is that
21 right? The physical presence is required?

22 CHAIRMAN MCGUIRE: No, you see the film at that
23 training session.

24 MR. TREACY: There is no--there really--we would
25 like you to come to this meeting. And you've all agreed to

1 Then today, I was really impressed with the
2 speakers, that they had lots to tell us about psoriasis that
3 was echoed by the committee. It seemed that generally
4 everyone had the same kind of experience. And I think I
5 took away three C's out of it. Rob Stern talked about it's
6 common, and everyone talked about it's chronic, and many
7 folks talked about the expense involved, it's costly.
8 Common, chronic, costly. And so it was a very relevant
9 topic for us to try to think through what the strategy
10 should be for deciding what the bar should be for approval,
11 and also elements that we can craft into the labeling that
12 will be truly informational to the patient and the
13 physician. And I think you've helped us a lot on that.

14 Thanks.

15 CHAIRMAN MCGUIRE: We're adjourned.

16 [Whereupon, at 3:09 p.m., the meeting was
17 adjourned.]

18

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CERTIFICATE

I, **THOMAS C BITSKO**, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceeding 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', written over a horizontal line.

THOMAS C. BITSKO

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