CENTER FOR DRUG EVALUATION AND RESEARCH

FOOD AND DRUG ADMINISTRATION

FORTY-SEVENTH MEETING

OF THE

DERMATOLOGIC AND OPHTHALMIC DRUGS ADVISORY COMMITTEE

8:37 a.m.
Friday, September 5, 1997

Versailles I and II
Holiday Inn
8120 Wisconsin Avenue
Bethesda, Maryland

APPEARANCES

COMMITTEE MEMBERS:

JOSEPH McGUIRE, JR., M.D., Chairman
Carol Herzog Professor of Dermatology
and Pediatrics
Stanford University School of Medicine
Department of Dermatology
MSLS Building, Room P-204
Stanford, California 94305

TRACY RILEY, Executive Secretary
Advisors and Consultants Staff
Center for Drug Evaluation and Research
Food and Drug Administration
Chapman Building, Room 200
5600 Fishers Lane
Rockville, Maryland 20857

SUSAN COHEN, B.S., Consumer Representative
3814 Inglemere Drive
Bethesda, Maryland 20817

S. JAMES KILPATRICK, PH.D.
Professor of Biostatistics
Medical College of Virginia
Virginia Commonwealth University
1101 East Marshall Street
Sanger Hall, Room B-1-039-A
Richmond, Virginia 23298-0032

JOEL MINDEL, M.D.
Director, Neuro-Ophthalmology
Mt. Sinai Medical Center
Annenburg Building 22-14, Box 1183
New York, New York 10029-6574

MILTON ORKIN, M.D.
Clinical Professor
Department of Dermatology
University of Minnesota
2733 Huntington Avenue South
Minneapolis, Minnesota 55416

APPEARANCES (Continued)

SPECIAL GOVERNMENT EMPLOYEES, CONSULTANTS AND GUEST SPEAKERS:

WILMA BERGFELD, M.D.
Head, Clinical Research
Department of Dermatology
Cleveland Clinic Foundation
9500 Euclid Avenue
Cleveland, OH 44195-5032

COLIN CRAWFORD, M.B., CH.B., MRCP, DTM&H
Neuromuscular Diseases Department
Division of Neuroscience and
Psychological Medicine
Charing Cross Hospital
Fulham Palace Road
London, United Kingdom W6 8RF

KEN HASHIMOTO, M.D.
Professor and Chair
Departments of Dermatology and
Syphilology
Wayne State University School of Medicine
4201 St. Antoine
Detroit, Michigan 48201

W. CHRISTOPHER MATHEWS, M.D., M.S.P.H.
Antiviral Drugs Advisory Committee Member
Professor of Clinical Medicine
University of California at San Diego
Medical Center
Mail Code 8681
200 West Arbor Drive
San Diego, California 92103-8681

O. FRED MILLER, III, M.D.
Geisinger Medical Center
North Academy Avenue
Danville, Pennsylvania 17822-1406

APPEARANCES (Continued)

SPECIAL GOVERNMENT EMPLOYEES, CONSULTANTS
AND GUEST SPEAKERS: (Continued)

CYNTHIA MOORE, M.D., PH.D.
Birth Defects & Genetic Disease Branch
Centers for Disease Control and
Prevention, MS-F45
Atlanta, Georgia 30333

EDWARD J. SHANNON, PH.D.
G.W. Long Hansen's Disease Center
P.O. Box 20572
Baton Rouge, Louisiana 70894

EVA SIMMONS-O'BRIEN, M.D.
Drugs Assistant Professor of
Dermatology and Internal Medicine
Johns Hopkins University School of Medicine
550 North Broadway, Suite 1002
Baltimore, Maryland 21287-0900

RANDOLPH WARREN
CEO
Thalidomide Victims Association of Canada
P.O. Box 9061 sub 40
London, Ontario
Canada N6E 1V0

FOOD AND DRUG ADMINISTRATION STAFF:

DENNIS BASHAW, PHARM.D.
Biopharmaceutist, Division of Pharmaceutical Evaluation III

DEBRA BIRNKRANT, M.D.
Acting Director, Division of Antiviral Drug Products

MURRAY LUMPKIN, M.D.
Deputy Center Director for Review Management, CDER

KATHRYN O'CONNELL, M.D.
Medical Reviewer

APPEARANCES (Continued)

FOOD AND DRUG ADMINISTRATION STAFF: (Continued)

BRENDA VAUGHAN, M.D.
Medical Reviewer

MICHAEL WEINTRAUB, M.D.
Director, Office of Drug Evaluation V

JONATHAN WILKIN, M.D.
Director, Division of Dermatologic and Dental Drug Products

JANET WOODCOCK, M.D.
Director, Center for Drug Evaluation and Research

CELGENE REPRESENTATIVES:

ROBERT H. GELBER, M.D.
KAREN KOOK, PH.D.
THOMAS REA, M.D.
STEVE THOMAS, PH.D.
BRUCE WILLIAMS
LEO YODER, M.D.
JERRY ZELDIS, M.D., PH.D.

ALSO PRESENT:

ALLEN MITCHELL, M.D.

C O N T E N T S

P R O C E E D I N G S

(8:37 a.m.)

DR. McGUIRE: Good morning. If the advisory committee can be seated, we'll begin our work.

This is the second day of the 47th advisory committee meeting of the Dermatologic and Ophthalmic Drugs of the Food and Drug Administration.

This morning we will have an open session, and rather than charge the committee, I will ask Tracy Riley, the Executive Secretary for a 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 and information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting.

With respect to FDA's invited guest speaker, Mr. Randolph Warren, he has reported interests which we believe should be made public to allow the participants to objectively evaluate his comments. Mr. Warren would like

to disclose that he has on two occasions discussed Synovir, thalidomide, with the Celgene Corporation.

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

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

We have on the committee four temporary voting members who are special government employees: Dr. Wilma Bergfeld, Dr. Ken Hashimoto, Dr. Fred Miller, and Dr. Eva Simmons-O'Brien.

Thank you.

DR. McGUIRE: Some of the faces around the table are different this morning, and I'd like to again have people introduce themselves, starting with Mr. Warren on the end.

MR. WARREN: I'm Randy Warren of the Thalidomide Victims Association of Canada.

DR. SHANNON: E.J. Shannon, the Gillis W. Long Hansen's Disease Center in Carville, Louisiana.

DR. CRAWFORD: I'm Colin Crawford, Imperial College School of Medicine.

DR. MOORE: Cynthia Moore, Centers for Disease Control and Prevention.

DR. MATHEWS: Chris Mathews, University of California, San Diego.

DR. MINDEL: Joel Mindel, Mt. Sinai Medical Center, New York.

DR. ORKIN: Milton Orkin, dermatology, University of Minnesota.

DR. BERGFELD: Wilma Bergfeld, dermatologist, the Cleveland Clinic.

DR. McGUIRE: Joe McGuire, dermatology, pediatrics, Stanford.

MS. RILEY: Tracy Riley, Executive Secretary to the committee.

DR. SIMMONS-O'BRIEN: Eva Simmons-O'Brien, dermatology and internal medicine, Johns Hopkins.

DR. KILPATRICK: I'm Jim Kilpatrick, School of Medicine, Medical College of Virginia, Richmond, Virginia.

MS. COHEN: Susan Cohen, consumer member.

DR. HASHIMOTO: Ken Hashimoto, dermatologist, Wayne State University in Detroit.

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

DR. BIRNKRANT: Debra Birnkrant, Division of Antiviral Drug Products, FDA.

DR. WILKIN: Jonathan Wilkin, Division of Dermatological and Dental Drug Products.

DR. WEINTRAUB: Mike Weintraub, Office of Drug Evaluation V.

DR. WOODCOCK: Janet Woodcock. I'm head of the Center for Drug Evaluation and Research at FDA.

DR. LUMPKIN: And I'm Murray Lumpkin, the Deputy Center Director at the Center for Drug Evaluation and Research, FDA.

DR. McGUIRE: Welcome to all of you.

The major work of the day is to answer questions that were generated by the agency, and before I do that, because of mailing issues and various problems, the briefing books were not received by all the members of the advisory committee in a timely way. So, I'm afraid that the reviews of the primary and secondary medical officers may have been overlooked, and I would like to ask either one of them, Dr. Vaughan or Dr. O'Connell, to go over their conclusions and a little bit of the background material, if they would, and then we could have some discussion of that.

DR. VAUGHAN: Good morning. Just bear with me. I'm a little nervous. I wasn't quite prepared to give a

presentation this morning. I was prepared to possibly answer questions.

The application was unique in that, as presented by the sponsor, Celgene, there was a retrospective review of a published controlled clinical trial conducted by Hastings, et al. at the Carville U.S. Public Health Service site in Louisiana. The study is called L-001.

In my review, I approached it -- I looked at the published report. I looked at the results that were given, the data -- well, not at the data. I looked at the results of the published report, and then I looked at the data as extracted and presented by the company.

There were several problems with the study as presented. There was no protocol provided and the randomization code was lost, but we were informed that Hastings had provided Celgene with information for patients that were identified between 1967 through 1969, were identified as the original study group.

However, there were difficulties with the information as presented, and some of the results had to be inferred and some of the randomizations had to be inferred.

There were problems with the verbatim transcriptions that were provided in assessing success or failure.

There were problems with the results as reported in the published paper and those that were presented by the sponsor.

There were incomplete data sets and there was difficulty with the data validation.

I don't know how many of you were able to read the review.

However, I have as one example some of the problems that I did have with the review and why I reassigned some of the patients.

This patient had been deemed a success in the review. However, this illustrates the difficulties and why I excluded this patient. This patient did not have on-study evaluation. I did not know if the patient had actually qualified for study entry as written. The temperature chart was provided, but there were not the required temperature elevations above 99.6 at entry. However, the patient did spike temperatures on day 1.

This patient also presents a problem with the assignment of which group, whether the patient was in the active or the placebo group. One of the main difficulties is that assignment was made from bottle A, and bottle A could contain either the active drug thalidomide or placebo. So, therefore, without the code, it would have to be inferred.

Now, some of the trials did show evidence of -- well, you could glean evidence of blinding. Some did not. So, this patient was excluded from my reassessment of the -- was not included in the efficacy analysis.

Additionally, there were problems with data validation. This patient 1707 was assumed to have been on thalidomide and successfully completed because the progress notes said two courses A. However, when the actual record was provided by the company, this assignment could not be gathered. It's very difficult to read but the assignment was from the 6/15/68, and the note continued to the second page, could not say that this patient had received two courses A. It was not there.

For some of those patients that I could see that blinding was evident was patient 2643, and this patient illustrates some of the difficulties I had with validation of the published results.

The published studies gave the results of single and double-blinded studies. We were to look at the double-blind studies only. The results of the published study, although this is not a critique of the study -- I'm just giving what was presented. The published study stated that there were no placebo successes. However, this demonstrates that under the date of 1/22/68, it did give the impression that this had been a double-blinded study.

Just found out patient was not receiving thalidomide, but rather placebo. His improvement is doubly astounding.

The published report gave 0 successes and clearly there were 3 successes as provided by Celgene.

There was a problem with the verbatim transcriptions since we have to infer which group that the patients belonged to. Patient on thalidomide once more. Has been afebrile times 2 days. This made a difference in the patient assignment. That was from the actual record. The date was 3/18 -- 3/15 -- 3/18.

Patient on thalidomide once more. Has been afebrile plus 2 days. No more ENL. This is different from the transcription, although the words are the same. The reason I reassigned this patient to the thalidomide group was because of the patient on thalidomide once more, which then with the period here, it refers to the thalidomide and not to the febrile episode. I was able to count back and reassign the patient.

The other problem with the verbatim transcription was what was provided. One instance that I noted was that the nurse's note was provided in the safety assessment as opposed to the doctor's note which provided vital signs, and this particularly would have been useful information given the systemic nature of the ENL.

Additional problems that I had with this

submission was the validation of the data. There was a patient that was listed as having expired prior to entry until the double-blind study. It's patient 2253. However, when a request for the actual records, the patient did receive thalidomide, four doses, -- the dates are up here -- on January 29th.

The listing that was used to identify the patients was later identified -- Dr. Yoder informed us that this listing could not be used as an official listing because it was kept by a non-medical person.

With the reassessment of the patient outcomes of the patients that I did include in the review, I could not find that the evidence as presented demonstrated efficacy.

Safety assessments. I was not able to glean a successful -- an adequate safety profile because I was not sure of what information had been transcribed and which had not. I did not have time to review the primary patient records.

DR. WOODCOCK: Could I clarify something about this?

DR. VAUGHAN: Yes.

DR. WOODCOCK: Just to make sure that everyone is clarified. My understanding of what happened here is there was a published report of the experience. The

clinician had used courses of either placebo or treatment, and that was historically collected over quite a while. Is that correct? And that the primary record keeping that was done for this study was not obtainable at the time that the firm went back to obtain the records. So, what you had to do and the firm had to do was try and reconstruct the course of the study from the primary patient records. Is that an accurate description?

DR. VAUGHAN: I'm not understanding.

DR. WOODCOCK: Were the actual case report forms of the study obtainable for you?

DR. VAUGHAN: The actual case report forms?

DR. WOODCOCK: Yes.

DR. VAUGHAN: From the study.

DR. WOODCOCK: Yes, from the study itself.

DR. VAUGHAN: I'm not sure what Celgene had access to. I was not presented with that.

DR. WOODCOCK: My understanding from the review is that those records were -- yes, maybe the firm could -- I think we need to clarify what was done here. There was a published report and there was an attempt to verify the data in the published report.

DR. KOOK: I'll just give a few words on basically how the data collection went. I'm Karen Kook.

DR. McGUIRE: Could you identify yourself for

the transcriptionist?

DR. KOOK: Yes. Karen Kook, regulatory advisor to Celgene.

When we became involved with Dr. Hastings, we were interested in collecting supportive documentation to support this particular published clinical trial. It was a placebo-controlled trial that was conducted in 1968 and 1969, published in the beginning of 1970.

Dr. Hastings, who was involved in the initial setup of the data collection, indicated that all of his records pertaining to this trial, such as his original case report forms, his original protocol, his original randomization, were lost.

In assisting us to identify the patients involved from the Carville medical records -- these are medical records for patients who were hospitalized or who resided at Carville at that time. I believe there are probably 3,000 medical charts there. I'm not quite sure. But to assist us in identifying those patients who may have participated in that trial, what we were given was a multi-page typed listing that had patient numbers, that also had patient dates when they received thalidomide. There were certainly discrepancies between those dates and the dates, once you looked in the medical records, whether it was nursing notes or doctor's orders, from when they received

thalidomide.

But nonetheless, we went through all of those charts to attempt to identify patients that participated in this double-blind trial.

Dr. Hastings initially conducted a single-blind trial using thalidomide with a product that was provided by Merrell Dow. There were probably a half a dozen patients whose orders for thalidomide referred to MRD730, or whatever the code name of the drug was. We kept a listing of those numbers of patients but did not attempt to collect any information from them.

It is clear also that he did in a single-blind fashion treat some patients with what he identified as thalidomide. But there were 27 patients who had in their medical charts in the doctor's orders section a one-page, typed-up study sheet that contained all of the instructions for how the patients were to be treated in this particular trial, and that included withdrawing whatever medications they were on to control their ENL, whether it included prednisone in some patients, analgesics, antipyretics, what have you. Patients were observed for a 4-day period of time off of anti-ENL treatment.

He had his criteria for initiating double-blind treatment and patients did begin on bottle A. Unfortunately, bottle A either contained, as Dr. Vaughan

indicated, thalidomide or placebo capsules. So, it was not very easy to decide what these patients were receiving. They received double-blind medication for 4 days and then were either crossed over to bottle B, which again contained the alternate treatment, but it was not that -- one had to extrapolate, and then continued some on single-blind treatment. And there were periods when they ran out of medication, so they were on single-blind placebo, what have you.

What we did was transcribed progress notes, and what Dr. Vaughan was the electronic version of our transcription of those records beginning on day minus 4, which was when their treatment was discontinued, on through the double-blind period and for varying lengths of time, either until open-label thalidomide was discontinued or up until about the time of publication.

A lot of these patients actually continued to receive thalidomide for many years and we did not attempt to collect that entire experience. What we really were trying to focus on was the double-blind phase.

We created a series of listings. Dr. Vaughan showed the listing for patient 1707, and it illustrates how we approached doing this. There are many ways that you can do it. The intent was not to extrapolate based on looking at the data and coming to our own decision. What we were

looking for were words of Dr. Hastings that indicated what his judgment at that time had been.

So, patient 1707, you could see that there were not progress notes for every day, but on day 6, or whatever day that was, he had in his note written, success on thalidomide, or whatever it was. When we saw that, we would have categorized that as a success. We did not sit down and make our own independent judgment, and created listings that gave what the basis for that judgment was. One can certainly debate the treatment attribution for every patient.

We created similar listings -- and Dr. Vaughan showed an example of that -- where because we were extrapolating from records to attempt to decide what patients were receiving, again we created listings so that one can, to the extent possible, independently decide whether one disagrees or not.

And then there was a third listing for text taken from the notes that could have represented adverse events.

I have looked at Dr. Vaughan's review quickly, and while I haven't had a chance to go through all of the cases, but there are 18 patients for whom her assessment of treatment response and our assessment does overlap. Basically this is what it looks like, that roughly two-

thirds of the patients on thalidomide by this approach would have been considered responders as compared to one-third of the placebo patients.

Dr. Vaughan did show an example of one of the patients that was a placebo responder. That is in the medical record. That is how we reported that patient. Why Dr. Hastings did not include that patient in his publication I have no idea. It's not surprising to me that the numbers do not match up.

Our intent was to validate that these patients existed, that yes, this was a double-blind trial. This is fairly representative of what we believe the outcome of this particular study was.

DR. McGUIRE: Thank you.

Yes, Dr. Miller.

DR. MILLER: Could I ask one question? When you said that 18 were responders, what do you think the criteria were for response for a positive response. Did you look at Dr. Hastings' note which said patient improved? But what were the criteria that you could glean from there that would indicate a response?

DR. KOOK: The publication stated that patients had to be afebrile after 4 days of treatment and to have no acutely inflamed lesions. He did not address the other systemic manifestations of ENL.

And I don't have an overhead of this. If you look at the mean temperatures during the 4 days prior to initiation of double-blind treatment, you can see that the temperature is steadily increasing, and following the implementation of double-blind treatment, it basically is sort of an inverted U-plot.

Again, because we were focusing on his publication, we did not address any of the other symptoms that the patients may have had, but you can see from the notes that they were relatively brief.

DR. McGUIRE: Dr. Wilkin?

DR. WILKIN: Well, I think the sponsor is correct in that you can go back through and look at where you can assign individual patients.

But the continual reference to this being a double-blind study I think the committee needs to interpret. The placebo was not a sedative and the amount of thalidomide being given likely would break the blind in this particular study.

Then Dr. Vaughan also was the reviewer for E-002.

DR. VAUGHAN: This was my reassessment of the patients from the data that I was presented and my findings were different from the sponsor's findings with my reanalysis of the patients.

DR. McGUIRE: Dr. Kilpatrick?

DR. KILPATRICK: I have to say that I find this discussion moot, and I'd like to say why and ask the FDA whether I'm wrong on this.

I'm coming to the Philippine study where we were told by the sponsor that FDA had agreed that this should not be a placebo-controlled trial which implies to me that the FDA had accepted that thalidomide was effective, perhaps not Synovir, but thalidomide in other formulations.

DR. WILKIN: Yes. I can say that from the discussions with the group from Celgene over the last two years, that we were given the strong impression from them and from their consultants. I believe that the leprologists who are their consultants sincerely believe that thalidomide does indeed work, and I believe that Celgene believed that when they looked into the database, looked into the Hastings study, looked into the vast amount of data that was at Carville, that they would indeed find that this was the case.

On that basis, yes, we did request that they do placebo, but they could not find leprologists who were comfortable with placebo. I think you heard their argument for no placebo yesterday. It was on an ethical basis. They believed they had convincing information that they

were not prepared at that time to actually convey to us. It wasn't in that particular form. Frankly, we didn't see data on this until the NDA submission.

DR. McGUIRE: I'd like to hold other questions for just a moment.

Dr. O'Connell, did you want to respond to any of this or did you want to give your conclusion of your review of the submission?

DR. WILKIN: Could she speak to E-002 just briefly?

DR. McGUIRE: I can't hear you, John.

DR. WILKIN: Dr. Vaughan reviewed E-002 and she has spoken currently about E-001, and maybe if she just said a couple of words about E-002. That was that really vast database that the sponsor was referring to.

DR. VAUGHAN: Study L-002 was a retrospective look at a 16-year experience under IND 11,359 sponsored by the U.S. Public Health Service. The sponsor collected data, as I understand it, as entered into a database at Carville. My understanding is that the company did not have access to the case report forms in this instance.

The problems that I found with the review of L-002 was that there is not a known current protocol that is being followed, and maybe one of the major problems was the way in which the data were collected and entered into

the electronic database.

This is a sample of the annual case report form that was revised in 1978, and the difficulty with the reporting is that the dose of thalidomide is the mean dose of thalidomide taken during the year. It was difficult for us to make an assessment using mean dose on an annual basis.

Additionally, the safety profile of thalidomide was collected in a way that we usually don't collect for clinical trials. However, this was not intended initially, I imagine, to be reviewed as a clinical trial. But the side effects due to thalidomide only were reported and the laboratory abnormalities due to thalidomide only were reported.

The response to thalidomide was collected, but without a protocol, it was unknown exactly what criteria were being used.

Again, it was difficult to determine whether there was adjunctive therapy or monotherapy from the database because previous therapy for ENL was listed, but not necessarily adjunctive. Even if adjunctive therapy had been listed, as I understand it, if the drug were not considered experimental, they were not necessarily entered into the database.

During the 16-year period, the source of

thalidomide also varied, and this presented a problem with then the selected adverse events recorded. There was one death recorded during the 16-year experience, and this may have been due to the selective nature of the reporting. I don't understand why there were no other deaths reported.

As far as the safety data is concerned, we looked at the reports of neuropathy as reported.

DR. McGUIRE: This is Dr. O'Connell who was the secondary medical reviewer.

DR. O'CONNELL: As Dr. Vaughan pointed out, it wasn't totally clear that we were not just going to be answering questions, to give a presentation. Actually I'd like to ask Dr. McGuire. I have two ways I can do this. I could sort of give an overall picture of how we approached this through each study and then people could specifically ask questions about the specific study they're interested in. Or I can just pick here and sort of go through. I think it will take longer that way. Which do you think would be most helpful?

DR. McGUIRE: You're offering me the short way instead of the long way.

[Laughter.]

DR. O'CONNELL: You'll take the short way.

DR. McGUIRE: That will get me every time.

No. I think we've heard some of the

reservations that Dr. Vaughan had about the review. I think you should just pick up a few points and then we could question. There will be questions from the advisory committee.

I think the important thing to the advisory committee -- well, there are a lot of important things, but several people on the committee did not have this information to review before we came here. After you've made a few comments, I'd like for Dr. Wilkin to comment, and then there can be general questioning before we go into the questions.

DR. O'CONNELL: Okay. Then why don't I try the approach. It's essentially the approach that I took. I think in most cases I'm speaking for both of us, but I'm speaking for myself. She'll let me know if I'm not speaking for her. I'll give you the overview and then if you want details, I've got some overheads I can pull out.

The way I approach an NDA submission is I look at the proposed indication, and then I go through the data sets in the application and I ask myself does the information in the data set support the proposed indication.

Now, the proposed indication that was submitted for our review stated was that thalidomide is indicated for the acute treatment of moderate to severe ENL, erythema

nodosum leprosum, that is characterized by signs and symptoms such as neuritis, orchitis, uveitis, nephritis, extensive cutaneous lesions that may be ulcerating, and high fever. Thalidomide is also indicated as maintenance therapy for prevention and suppression of ENL recurrence.

So, I'm just going to briefly go through the four or five data sets that we had and just say why I didn't feel that the information was sufficient to allow me to make a conclusion one way or the other about this proposed indication, including orchitis, uveitis, nephritis.

Dr. Hastings' study, L-001, as Dr. Vaughan and Dr. Kook just described, addressed skin and fever, cutaneous lesions and fever, and then L-002, the second study, which is the extensive IND experience.

As far as we could determine those responses that Dr. Vaughan just showed -- good, fair, poor, whatever -- pertain to skin. Please, I invite the sponsor. If we didn't understand it correctly, please let us know.

DR. GELBER: It was not entirely clear what everyone did, but I can only say what I know that I and Tom Rea did. That is, those that were judged good did not have anything other than an occasional skin lesion or rare skin lesion. So, those that had more than that, either many skin lesions or fever or other manifestations -- so, I

think that we were looking at other more significant aspects of the ENL syndrome.

DR. O'CONNELL: Well, let me restate that then. Again, if there's more information, we would like to hear it.

We were not able to really find, though, any actual data about the other manifestations. Did we miss it? In the IND database.

DR. KOOK: If you're referring this to the Carville IND experience specifically, if Dr. Vaughan had showed the one-page case report form where it stated the categorizations of response -- it was stated as good, fair, poor I believe, no response, and what have you -- that was the extent of what has been collected on an annual basis under this IND. What Dr. Gelber described for you is how he as a clinician who probably treated -- I don't know -- a quarter of these patients applied this type of a global rating to his judgment of the response of the patients.

My own interpretation of it is that it was not intended to apply only to skin lesions. It is a global clinical assessment of how these patients were.

DR. O'CONNELL: Okay, thank you.

Then the L.A. data which was collected from one site under that Public Health Service IND, in order to try to get us more information, because of the issues that Dr.

Vaughan has already discussed and the sponsor discussed about the dosing being given as means and other issues. So, the L.A. data was collected. As Dr. Weintraub said yesterday, basically the database that the agency generated from those patient charts captured parameters relating to the cutaneous manifestations of ENL.

Then the other data set that we had available to us was the published studies. There were five controlled published studies in addition to Dr. Hastings' study, and some of them did address systemic manifestations of ENL.

In particular one study, Dr. Iyer's study, which was sponsored by the World Health Organization -- I think it was published in 1971 -- contained a lot of very good data. I think it was in your packet. We specifically included that paper.

The problem is, I think as several people have pointed out yesterday, the people who wrote those very nice papers never looked forward to 1997 and thought that we'd be sitting in this room trying to reconstruct the sources, the information that we generally need to make a regulatory decision. We didn't have source documents for any of the published studies except for Dr. Hastings' study.

I'll just use Dr. Iyer's study as an example. Even though it contained a vast amount of very useful

information and actually some very maybe interesting clues about what kind of trials could be done, the inclusion criteria for the systemic manifestations, as well as the skin manifestations, were not defined in detail. In other words, he would list, if you've got the paper there, in a table nerves or lymph nodes. So, it wasn't really clear to us what level of severity or how those things were assessed or how they were assessed in the course of the study.

So, while the information is helpful, at least I didn't really feel that I could make a regulatory decision about that indication which included those serious systemic manifestations of ENL based on those studies. I think it's a very important point because, as we've heard from the experts on leprosy, uveitis, orchitis, nephritis, neuritis, if those conditions aren't adequately treated and in a very timely manner, the patient suffers very serious harm. So, I was very rigorous in my thinking about the data.

Then I would come to the sponsor's ongoing dose comparison trial which, as everyone has pointed out, is still blinded, so we don't know how results will stratify by dose. There are two doses, 100 milligrams and 300 milligrams.

Again, the initial NDA submission contained data for 9 patients, and that's what's in my review that

you have that says Secondary Medical Officer's Review, and it's dated I guess August.

Then last Thursday we received data for 7 more patients and 1 additional patient who, as the sponsor pointed out yesterday, did not have any skin lesions. The patient was apparently enrolled with severe neuritis, but no skin lesions.

Again, please correct me if I'm wrong because I'm sort of merging those two reviews and pieces of data in my head right now.

But by my count, and like I said in my review of the draft information on the additional patients that we got Thursday -- it was in draft form. I did not have time to really go through the systemic manifestations of ENL because the draft material that we received was line listings essentially and tabulations, no formal analysis, no narrative type information. We appreciated the information very, very much. It's just that I didn't have time to go through the systemic manifestations yet, but I'll get to the cutaneous in a minute.

But anyway, by my count, it appears that in this E-003 database to date -- and like I said, the study is ongoing, so there will be more information later -- I didn't find any cases of uveitis or nephritis. Is that right? Okay.

In the draft database, there was one case with mild orchitis, and I think there are four cases with neuritis at baseline. I think that's right. The one was severe neuritis in the draft and then there was three in the first group with mild to moderate neuritis at baseline.

There's also I think 2 patients -- and correct me again if I'm not remembering this right -- in the first set of patients who had neuritis listed, but it wasn't listed at baseline. It was listed like on the first or second day on drug.

DR. KOOK: In fact, you got the listings before I did, so I've had less time to look at it.

There were 5 patients who had neuritis at baseline.

DR. O'CONNELL: Five?

DR. KOOK: Yes, in the 17-patient updated data set.

Dr. Cornblath yesterday put up a slide -- and unfortunately he's not here today, nor do I have a copy of it -- where all of the case report forms that pertain to the neurological evaluation of these patients were provided to him for his review. In essence, patients had a neurologic exam at baseline that included sensory and voluntary motor testing. They were questioned daily for paresthesia and numbness. These patients were seen daily

in the clinic, and they continued to be seen daily throughout the tapering period, but with formal case report form assessments weekly during the 6-week taper.

If I remember his presentation yesterday, his overall conclusion was that roughly half of the patients had improvement in their neurologic symptoms during the 7-week period of time.

There was 1 patient who comes to mind who on day 4 or 5 did answer yes to the questions whether or not he had paresthesia and numbness during the trial, but other than that, there was no persistent symptoms in the remaining 5 patients. So, there was that one transient observation.

DR. O'CONNELL: Like I said, please step in if I misinterpreted this. There was actually 1 patient -- I don't want to get into minute details here, but there was 1 patient -- I have here patient 5 -- who had mild neuritis present at baseline. Patient 5, by the way, was coded by the sponsor as a treatment failure. Then it was coded as moderate on drug at the end. So, the neuritis got worse.

I was also wondering, since it was a draft and we haven't had time to really get together about it yet, about the patient that was enrolled in the new group with the severe neuritis but no ENL lesions. Do you have any more information? It said in the submission I think that

at the end of the 7-week tapering period it had resolved, but I was wondering how long. Do you know how long it persisted?

DR. ZELDIS: She actually saw the patient.

DR. KOOK: We have a case summary written by the investigators of the patient. I don't have it with me unfortunately.

This patient had in the past had episodes of ENL that included skin lesions, fever, what have you, and at this particular time was not being treated for ENL, had had a fairly persistent nerve enlargement that was tender, that was warm. It was literally the size of a pencil.

The investigators decided that they would treat him with thalidomide even though he did not have lesions and fever. Within a couple of days, the size of the nerve was reduced. It was still enlarged at the end of the trial, but the tenderness was gone and he had no other fever. He had no other signs of ENL during that period of time.

DR. O'CONNELL: Was he treated with prednisone for the neuritis?

DR. KOOK: No, no.

DR. ZELDIS: The patient who had orchitis, if you look at the 7-day shift table and the comparison, you'll see that he was absent on day 7 as well. So, that's

why yesterday, when I presented the data to the study, I did say that some people were worse. These were the treatment failures. But all those symptoms, if you go to what happened at 7 days, they all were absent. That's why I can make that statement. And you have the data.

DR. O'CONNELL: Can I ask you just one other question? If you want me to move on --

DR. KOOK: I'll make one other comment about the prednisone because the --

DR. McGUIRE: Let me get things a little bit under control here. A little chaos is good. A lot of interesting things come out, but where are we going?

DR. O'CONNELL: Okay.

DR. McGUIRE: Do you have more in your presentation?

DR. O'CONNELL: That's basically 003. That's the information for the systemic manifestations.

Now, in the sponsor's presentation yesterday, I noticed that the proposed indication has changed. I couldn't really get it down in the exact words, but I seem to recall that the systemic manifestations, the signs and symptoms, were not in there anymore. As Dr. Wilkin pointed out yesterday, the term "ENL" can refer to ENL skin lesions or it can refer to the syndrome of ENL. So, I think that a clear understanding of the indication -- oh, thank you.

The new indication is thalidomide is indicated for the acute treatment of erythema nodosum leprosum as well as for maintenance therapy for prevention and suppression of ENL recurrence. Then it says, dose: acute, 100 to 200 milligrams per day at bedtime; severe ENL, 300 to 400 milligrams per day at bedtime.

So, I think in my own mind that a clear understanding of the indication proposed is critical to a regulatory decision for the reasons that I stated earlier regarding the systemic manifestations.

So, to move on here, I'll just do the same thing I just did but in terms of the cutaneous manifestations of ENL. So, the question is, does the evidence contained in the application -- did it allow me to make a decision either way about the clinical benefit for cutaneous ENL? And if so, for what level of severity of cutaneous ENL?

As I said in my review, I think that the issue of disease severity is important. It's important to my thinking about this drug because the drug can cause serious birth defects.

Now, I'll now go over the database again, just quickly, and ask whether in my mind they contained adequate information to address the severity of cutaneous ENL.

Dr. Hastings' study, study L-001. As Dr.

Vaughan pointed out, the entry criteria was freshly appearing lesions and fever, and that's basically it.

In study L-002, which is the IND database, as we saw earlier, the coding is good, very good, excellent, whatever. The definition that we found in the application -- and again, if we missed something, please speak up. The definition that we could find for "good" was as follows: "A patient in whom there was a very clear response to thalidomide and the patient was not sick, had no fever, but may have had a few bumps." So, again, I don't think that that information from the IND database gives me much information about the severity of the cutaneous disease that we're treating.

So, then again we went to the L.A. data set that the agency collected to try to get more information. As you saw yesterday, when Dr. Weintraub gave his presentation, the database generated captured three parameters relating to the cutaneous manifestations of ENL. One was ENL activity. One was ENL, present, absent, and one was ENL new lesions, yes or no. But it did not capture any quantitative or qualitative information about the lesions.

So, when you see a dot and it was new lesions and it goes from yes to no, when I reviewed that database, which is what I was given to review, the statistical

report, the scatter plots, I had no way to know whether that meant the patient had 2 nodules on their right arm or left arm that resolved or whether the patient had 200 ulcerating nodules that resolved.

Also, there's a list of assumptions that I made to review that in the review, and I won't go through that.

As Dr. Weintraub pointed out yesterday, it did not address concomitant aspirin or nonsteroidal anti-inflammatory drugs.

Then the published studies again, other than Dr. Hastings' study. One of the papers actually -- I think it was Dr. Waters' paper actually did have a six-point scale that was informative about the skin lesions, but there was sufficient detail as far as the results about the severity of the skin lesions that responded.

But in general, the published studies, because they're published studies and they weren't meant for the purpose that I tried to use them for, just in my mind didn't have sufficient detail regarding the number and the severity of the cutaneous lesions for me to make a judgment about what exactly it was that was resolving.

Then study E-003/P, which is the sponsor's ongoing trial, the dose comparison trial. As has already been pointed out this morning, doesn't have a placebo group, so it can't address the contribution of a placebo

effect or observer bias in assessing the lesions.

However, the protocol defines the primary endpoints as fever and the number and the quality -- the number and the quality -- of cutaneous lesions -- acutely inflamed nodules, pustules, and ulcers -- which is very useful information.

As I said before, there were results for 9 patients submitted originally and then the 7 additional patients with cutaneous lesions.

Now, again, I can answer questions about this later with some overheads, but for now, I'll just give you a brief overview.

The draft submission, as the sponsor pointed out yesterday, also contained updated data for concomitant medications. In reviewing the information, it's also important to note that the temperatures that were actually measured at the site were axillary temperatures. They weren't oral temperatures. The protocol, of course, calls for oral temperatures.

So, when I reviewed the material, I shifted the efficacy endpoint for the fever down by 1 degree. So, in other words, if the listing said that it was 98.7, then I took that to mean that the temperature was somewhere around 99.7 because it's an axillary temperature.

Also, the lesion counts were often approximated

at the site as like greater than 10, less than 10. Sometimes the entry was few, more, some. There was an algorithm. The way I understood it, the algorithm was created retrospectively and used to convert?

DR. KOOK: Yes. The lesions were counted by body region and they were counted as lesions that were acutely inflamed or lesions that were resolving. Face, head and neck I guess, trunk, right and left upper and lower extremities. When there were greater than 10 lesions, that's typically when they would put down greater than 10 lesions. If you tallied up the number of lesions, they all had more than 40 acutely inflamed lesions at baseline. Some of them had lesions in the hundreds.

Since that first interim submission, we did go back out to the site, and for some of those patients, if you went to the source documents, there were numerical counts for some of those. So, some of the "fews" have been resolved.

But in essence what we did -- and maybe you can help me -- just in order to come up with numbers, if they wrote down greater than 10 acutely inflamed lesions, we arbitrarily made that 12. If it said few, I think we called that 3. But that was something that we came up with as a way to assign numbers to some of these qualitative counts.

DR. O'CONNELL: So, my interpretation of that was that would work for me if all of the lesions in the 7-day period could be expected to -- in other words, if the therapeutic response that you'd expect was that the lesions would be totally gone in 7 days, then that would work for me because if they're gone, it doesn't really matter if you say there's -- it's nice to know how many there are, but if there's 100 and 100 are gone, 100 are gone.

But the problem is that ENL lesions don't just vanish in 7 days. There may be no more acutely inflamed lesions, but you can't expect the lesions that were already there to disappear, which was very helpful what the sponsor gave us to review in the original submission.

Like I said, the new submission is drafted and so it's not complete yet.

But in the original submission, we were given the number of acutely inflamed lesions, which is the endpoint, as well as the number of resolving lesions, which was very helpful because, if you think about it, the distinction between an acutely inflamed lesion and a resolving lesion is somewhat subjective. There's no machine that you can use to measure that. It's a clinical judgment. Because the trial is not a placebo-controlled trial, I had to think about the contribution of observer bias in that kind of subjective assessment.

Sometimes I had a problem because there would be more resolving lesions of a certain type than there were acute lesions preceding it.

But, nonetheless, in reviewing the line listings with those alterations in mind and taking into account the concomitant medications that were updated, I tried to group the responses according to the protocol at day 7. What I came up with was 4 complete responses out of those patients. Like I said, if you would like me to later answer any questions about why or how each patient fell into those groups, I'll be glad to.

Now, when the trial is completed and all the data are available and verified, I think that it may well inform the question of the efficacy of the severity of cutaneous disease because, as I said, the lesions are stratified by their type, ulcerations, pustules, nodules, and numbers, which is very helpful.

Then I'll just finish up by saying that the second part of my thinking about the clinical benefit was, of course, risk. I'm particularly concerned in this regard because the safety database for the sponsor's formulation, as I understand it, in leprosy patients is 28 patients. 28 patients is the number of patients that I have information on for the sponsor's product in leprosy patients, and 6 of those 28 patients received only one dose in the PK study.

As discussed yesterday, the Celgene formulation is more bioavailable than the older formulations.

And we also heard discussion yesterday about the relationship of dose of the drug to peripheral neuropathy. As you can see in my review, I'm concerned about the peripheral neuropathy. The information that was submitted in my mind didn't really allow me to make a conclusion of whether ENL patients are at risk or are not at risk for thalidomide-induced neuropathy.

The reasons for that are discussed in the review, and it has to do with the studies that have been published, the type of testing that was done in the studies that have been published, the lack of retrospective -- I mean, prospective electrophysiologic studies in leprosy patients, as was discussed yesterday.

The reporting problems for adverse events, as Dr. Vaughan alluded to. When we actually went through the database, the IND U.S. Public Health Service database, and excluded sedation and drowsiness, but looked specifically for neurologically related adverse events, we noticed that there was an apparent asymmetry in the reporting amongst centers where one center appeared to have like, I think it was, 42 percent of all the neurologically related adverse events. I don't know if those adverse events had anything to do with drug-induced peripheral neuropathy, but they

were things like paresthesia. It's in the back of the primary reviewer's review. It's a table. You know, burning sensation in the hands and feet, and some of them were leg cramps, whatever. So, I found it difficult to draw a conclusion either way as far as the risk of peripheral neuropathy in these patients.

In my mind, it's an especially important issue in this patient population because it's my understanding that the disease-related damage in patients with leprosy and ENL -- both problems, leprosy and ENL -- that the disease-related damage to the peripheral nervous system is one of the greatest causes of morbidity in these patients, and that even slight worsening might be functionally very significant for these patients.

DR. McGUIRE: What I'd like to do now, I'd like to ask the Division Director, Dr. Jonathan Wilkin, if he would comment on his review, and then we'll have questions from the advisory committee.

DR. WILKIN: Mine is brief. It's five pages. I can go just briefly through and comment on perhaps some of the things that have changed over the last several days.

DR. McGUIRE: Actually, Dr. Wilkin, could you start with your conclusions and work backwards?

DR. WILKIN: Sure. My conclusions are that I would recommend that this be non-approvable given the

current information for efficacy and safety for erythema nodosum, the systemic syndrome, and also for erythema nodosum leprosum, confined to the cutaneous lesions.

I do concur with the two medical reviews. At the time I wrote my review of theirs, I only had their initial reviews, but of course, subsequently Dr. O'Connell has written two additional brief reviews. I've read those, discussed those with her, I concur with those as well.

I was particularly struck by the extremely large databases the sponsor has described for E-002, the many, many patient-years of thalidomide and the kind of information we might be able to glean from it. It's not that we really have evidence so much that there are adverse reactions in that population. The difficulty is that we don't really have evidence of safety in that particular study.

My interpretation is that the investigators were only describing adverse events if they thought they could be attributed to thalidomide. Dr. Vaughan mentioned that there was 1 death in the 1,000-plus patients, many of whom were in their 50s, 60s, and 70s and had been treated for years with this drug. If that is truly the case that only 1 person in a population that large is going to die in that period of time, then we're talking about the wrong indication today. Longevity would be what I would be going

for. I think, though, that what really happened was the investigators were only calling things they thought were thalidomide-related.

The point has been made that a large signal emerged from the Staten Island thalidomide ENL population for neurotoxicity. The question would be, why was neurotoxicity seen in the 800 series of E-002? It may have been that the leprologist at that location was reporting neurotoxicity whether it was related to leprosy or to thalidomide, but was simply reporting it.

And it's a signal that needs to be teased out. We need to know more about that I think. Dr. Crawford has made the statement, and I think Dr. Cornblath agrees, that we really don't have really superior information at this point using the right kind of sensory nerve conduction studies prospectively to find out how much neuropathy really exists.

So, those were some of the things that I thought were very important from the primary reviews that I would mention.

I'm going down through the paragraphs. I still agree with the statistical review. I extracted some of the comments that the statistical reviewers had in their conclusion section.

The third paragraph, as I say, I do not concur

with the clinical pharmacology/biopharm review. That was the first biopharm review.

I now concur with the second biopharm review which Dr. Bashaw signed off on subsequently and has come to the committee. I think it was in your packages when you came. His second conclusion is, should approval of the Celgene NDA require use of the Tortuga database? Basically, with the exception of 28 patients, all we've talked about is the non-Celgene thalidomide database today. The applicant would have to demonstrate bioequivalency between the products.

Now, Tortuga and that particular lot of Tortuga is not the only thalidomide that was ever used to generate this database, and I realize that. But because of the strong bio-inequivalence signal, I would hope that the sponsor could find some other lots and that we might get a better feel for that relationship.

If there is bio-inequivalency, I'm not really sure how we're going to come up with good dosing recommendations using the data we've got. We know that the AUC and the Cmax, the very peak concentration and the area under the curve, are different for the two products and I don't think there's good pharmacodynamic, pharmacokinetic modeling. So, I'm not sure which one we would chase after if we were going after a dosing strategy based on that.

The methodological problems. I think the reviewers actually spent a lot of time talking about individual patients and how they would be assigned, and I think those are important considerations. I'm not minimizing that, but I think if you stand back and look at the database that we have received, because thalidomide is a very strong sedative, I believe that all of the studies in the literature are essentially unblinded and many of them may have been conducted by leprologists who have believed that they were simply coming up with the data to document what they believed to be the case, that is, that thalidomide works.

I think that that to me actually is one of the key troubling areas in this, that there is no such thing as a randomized controlled trial in the pure sense of the word for thalidomide. There might have been some opportunities in the past and today it would be very difficult with the two dozen patients that might be new patients in the United States each year.

But I would remind the committee -- and I have in here some examples of treatments in the past that haven't been just strongly supported by a handful of people but actually have been widely embraced, universally embraced. Insulin coma therapy for schizophrenia, the internal mammary artery ligation for angina pectoris, and

then the one I thought was probably most similar to what we might be thinking about with thalidomide is the penicillin plus sulfisoxazole for neonatal sepsis.

It turns out that the penicillin plus sulfisoxazole really did lead to a lower infection rate than the tetracycline derivative arm, but it turned out that, following those children, there was a much higher mortality in that particular group because of kernicterus.

I think that's the troubling part of thalidomide. Even if we can tease out and say, yes, this has a positive effect on the cutaneous lesions, we really need to know the whole picture to figure out whether we're really doing the right thing for the patients who have erythema nodosum leprosum.

I'm concerned about that population group. In the United States, that is a group in which many of them are Hispanic and Asian American immigrants. Some of them have document difficulties. I think it's a population that we need to be especially concerned about.

Others have described the steps that drugs will go through before they are finally debunked, if that's going to be what happens to them. I pulled this out last night, McKinlay's seven stages of a new therapy in the absence of well-controlled trials.

The very first stage is promising report. I

think we can identify when that happened for thalidomide for erythema nodosum in the 1960s with Dr. Sheskin's work. He was a very strong proponent and if you read the articles, I think you too would come away with the notion that this was very promising.

Then there is professional and organizational adoption, and it looks like the leprologists began using this and felt that indeed it really did work.

The third stage is public acceptance and state or third party endorsement. The World Health Organization I think in 1970 or 1971 described thalidomide for ENL, that it should be restricted to purely investigative uses, and by 1974 it was regarded as the drug of choice. I'm not sure who at the World Health Organization decided that, but it might have been a fairly small number of leprologists and it may well have been based on those papers that came out in 1970-1971, the early 1970s, and the Hastings study would be one of the studies. The Iyer study would probably be another study because that was sponsored by the World Health Organization.

Then at that point it became standard procedure, which is his fourth stage, and then there are some observational reports that maybe it's not working well for everyone or some people are having side effects with it. Then stage five is a randomized clinical trial. Then

stage six is professional denunciation, and stage seven is erosion and discreditation.

The idea is not to go through such a painful series of stages but to try to get a randomized trial. Even if it's a small trial, it can be controlled. It can be done better. Lesions might be counted rather than 3 to 5 being interpreted as 4, and few is 3, and that sort of thing.

So, I think trials actually don't have to be large. They don't have to have all of the bells and whistles that we expect for many of the drugs that we see that are much larger populations. But I do think that a better study can be designed than the E-003/P, the study going on in the Philippines, to answer these questions.

The other aspect that entered into how I formulated my thoughts on this is the off-label use. If there are two dozen new patients a year that are going to be using thalidomide for ENL, then that hardly seems to me to be a profitable market. So, the question is where is this really leading. I think that off-label use is where the vast majority of the use would occur. It would dwarf actually the use for ENL.

I'm concerned about the article written by Jacobson and his group that came out in May in the New England Journal of Medicine in which they studied patients

with aphthous ulcers who had AIDS, who were HIV positive. Some of the disturbing things that they found were the severe neutropenia, which is of course a special problem in that population, and the other is the increase in HIV RNA which suggests that maybe the HIV virus might be increasing in that particular group. My question is if it is available off-label, will the right kind of studies be done in the AIDS population to look at the increase in HIV RNA, and then also the question about neutropenia.

Now, I'm not a fan of the buyers' club. I would say that that's not a great idea, that we have great concerns about the purity of that product. It's coming to patients without labeling and I did think about that as well.

But when I put all of these things together, and especially I think about the patients with erythema nodosum leprosum -- I saw some of the slides yesterday that were the dot slides that actually look like some of these patients -- if you looked at the time axis, I think it was 600 weeks. I think I got that right. It looked like the patient was on thalidomide for a substantial period of that 600 weeks.

I really think we need to rethink thalidomide for ENL, come up with perhaps some different protocols, some better controls on ways to ensure safety, and look for

efficacy in this particular population, again which I think may be a compromised population in the United States.

There is no joy in recommending non-approvable. I have to say there is a sense of satisfaction when we in the division are able to recommend to the office or to sign off at the division level an approval because that means we've worked very effectively together with industry to bring a drug to the patients and physicians in America and to answer a medical need. And we all feel very good about that, but it's a very hollow feeling to recommend not approvable. But at this time, when I look at all of the aspects of this, that's where I would have to be.

My final comment would be I think it was a very important, wonderful moment for what Dr. Kelsey did many years ago. I also think it was an incandescent moment for the agency when our Deputy Commissioner requested industry to take another look at thalidomide. You saw my slides yesterday. I think there is potential in thalidomide as well. I would like to see that potential developed.

I know that the sponsor has worked hard to go back and look at a database. The database, as someone has pointed out earlier -- these are patient records. They were never intended to support proof of efficacy or safety. The sponsor took the challenge of the Deputy Commissioner and went with it and invested a lot of effort, and I admire

also what they did.

But again, at the end, my recommendation would still be not approvable.

DR. McGUIRE: Dr. Lumpkin?

DR. LUMPKIN: Joe, I just wanted to say one thing, since this is an open public meeting, we have members of the public here with us and perhaps some new members of the advisory committee here, just on process.

What you have heard, as Dr. Wilkin saying, when using the word "recommendation," the opinions that have been expressed are indeed I think the very heartfelt opinions of the reviewers and of the Division Director, but just you'll know the process, they represent their own personal opinions having looked at the data. That's what we employ these people to do, to look at the data, to look at it hard, to look at it critically, and to make a recommendation, but they are not the deciding officials. So, I just don't want there to be any misunderstanding within the public that what you've heard is, quote/unquote, the agency's recommendation. The agency has not made its mind up on this issue. That is why we are here today.

What the primary reviewer, what the secondary reviewer, what the Division Director have done is given us their opinions and that's part of the equation. What the sponsor has done is given us their opinion. That's part of

the equation. What you guys here at the table give us is part of the equation.

And I think it's going to be very important what happens the rest of this day to hear from you, the people that we've asked to come and represent the community, having heard what the recommendations are from the division, what the recommendations are from the sponsor, how you synthesize this and what your recommendation to the agency would be so that the deciding officials within the agency could then make the final decision on this.

So, just so people in the audience and newer members of the advisory committee would understand what the process is at this point.

Thank you.

DR. McGUIRE: Thank you, Mack.

What I'd like to do now is have the advisory committee direct questions toward Dr. Vaughan and Dr. Wilkin and Dr. O'Connell. Mrs. Cohen.

MS. COHEN: I'd like to add something because this is a very difficult thing. We have a guide to advisory committees, and I decided to review it again because I'm in a difficult situation because I am the consumer member. I mean, that sounds like I'm conceited. I'm not. I'm scared.

I listened yesterday to Mr. Warren and to the Women's Health Network, and I want you to know, in terms of the objectivity, that's what I'm supposed to be and I'm not supposed to have an intellectual bias. More than that, I have to tell you, although the FDA pays me to be here, they in no way influence what I think or how I think, and it would be very hard to do anyway, just with my personality.

But I want you to know I consider it an honor to serve here and I take it very seriously. As many of you know, my husband was a scientist and I grew up -- not grew up, but I lived with science for almost 43 years and I have great respect for it for what it can do.

So, I listen very hard and I don't want you to think, as a consumer member, I come in here, if it's industry, I'm just prejudiced. I'm not. It's a very difficult line for me to walk. And I worry. I do. I take it home with me. I worry. Although I might not have the disease, I do worry about the people who do, and when I vote, let me tell you something, it takes a lot out of me and I go home and I reflect and I reflect. So, I respect any company that comes and attempts to give us information.

I hope you don't mind that speech, but I felt it behooved me to say it as a consumer member.

I have a question, believe it or not. How much information can you get in a one-dose study? I've been

trying to figure that out in my mind. I've heard that it's very effective, even within 48 hours, but what does a one-dose study really tell you about thalidomide?

DR. O'CONNELL: Do you want me to answer that?

DR. McGUIRE: Sure.

DR. O'CONNELL: When I referred to the single-dose study, that was a pharmacokinetic study that Dr. Bashaw talked about yesterday.

MS. COHEN: Yes.

DR. O'CONNELL: To be honest, I'm not really qualified to comment.

DR. WOODCOCK: Can I answer in laymen's terms? Maybe that would be most helpful.

The single-dose studies, Ms. Cohen, are intended to show how the drug is absorbed out of the GI tract and how the body handles it after it's absorbed into the blood. So, it isn't to look at the effect of clinical activity of the drug.

MS. COHEN: Can I ask another question then, Dr. Woodcock? If one does a single-dose study, are there other things taken into consideration, the condition of the patient, what they might be taking, the interaction, and could you have a single-dose study that's an anomaly? Or do they do it on several people?

DR. WOODCOCK: Yes. It's done on several

people and we have massive experience with this because of our generic drug program where we approve a generic drug based on these studies where we show bioequivalence to the originator drug. So, we know about those factors.

Yes, you're absolutely right. They all have to be taken into account and there are ways to do that.

DR. McGUIRE: Susan, they're done with food, without food, different times of day, a lot of those variables.

MS. COHEN: But I noticed in what I read and what I reviewed -- and if the company would like to see all my red marks, they're welcome to do it because I did read and I read, for instance, that when they did it, they did it on some people who had fasted in some of their studies. Food must absolutely have a relationship to any kind of study that they do, as I understand it.

DR. McGUIRE: Dr. Bashaw?

DR. BASHAW: Traditionally pharmacokinetic studies are done in fasted individuals to minimize the number of variables that you're looking at. You're trying to see what patient factors are. You're trying to see effect of concomitant medications.

We also require, and the sponsor has done, although it was not contained in my review because it wasn't complete at the time my review was completed, a food

study. A food interaction study was looked at and a food study was done. Although I have only seen a summary of the information, basically what was seen is that the peak levels and the extent of absorption, the amount absorbed, was the same between people who took it with food and people who took it without food.

This is a very intense meal. It's a high fat meal. It's a couple eggs, whole milk. It's a great American breakfast. It really is.

So, those factors are looked at. It was not contained in my review because that study was not completed at the time. It has only been summarized now.

DR. McGUIRE: Are there other questions from the advisory committee? Yes, Dr. Miller.

DR. MILLER: Dr. O'Connell, in the eight records that you received that you reviewed, would you say again what you found in regard to the efficacy with the skin lesions? And how specific were the numbers, or did they just say acute reaction vanishing?

DR. O'CONNELL: From the ongoing trial.

DR. MILLER: Yes, from the present trial.

DR. O'CONNELL: I don't have overheads for the details of that. I have an overhead with the numbers. But I can tell you out of my review why I put people where they were.

Again, because the data just came in, we haven't had an opportunity to get with the sponsor and perhaps alter this. Like I said, if I've misinterpreted any of these records -- and like I said before, this data hasn't been formally analyzed or anything yet. This was based on my attempt to go through line listings and sort of cross reference various data from various charts and tables.

The way I came up with my efficacy categories was the patients that the sponsor did not analyze, I also agreed should not be included in there in the unassigned. Those were 3 patients who were re-randomized who had been previously treated, and 2 of those were treatment failures from the first group.

DR. McGUIRE: Is this 003/P?

DR. O'CONNELL: What did you say?

DR. McGUIRE: Is this the Philippine study?

DR. O'CONNELL: Yes. I'm sorry. 003/P.

The original submission did say that both of those treatment failures, as I think may have come out yesterday, that they did respond, that the investigator had given a verbal report that they did respond to 300 milligrams in an open-label use. Then when they relapsed, they were re-randomized. And the other re-randomization was patient 10 who was in the new group. So, I didn't

assign those.

I also didn't assign patient 4 and patient 16 who were both categorized as a complete response by the sponsor.

The reason I didn't categorize patient 4 at this time is that I think I need more information. The patient had no acute ulcers after baseline. I think the number of acutely inflamed ulcers at baseline was 28, and there were 75 nodules and 3 pustules acutely inflamed. But 28 acutely inflamed ulcers. So, there was none after baseline. So, the very next day they were gone. And there were no resolving ulcers at day 4. So, by day 4, even the resolving ulcers were gone. On days 5, 6, and 7 then the listing shows 48 resolving ulcers.

So, it's not clear to me if you can get resolving ulcers from resolving nodules because there also were no more acutely inflamed nodules. So, I think I just need more information before I can assign that patient.

Then patient 16 was coded as a complete response at day 7. Again, this is in the new group, so all the data is not there yet. And there was no data for the follow-up period, but the temperature at baseline was 96.9, which even if you put it up a degree to make up for the axillary temperature, that is 97.9. But in the ENL symptom assessment data set, that patient is coded on baseline the

same date with a moderate fever, and at day 7 the temperature was 98.7. So, I was not clear about the febrile status of that patient, so I didn't reassign that patient yet.

Like I said, both of those may end up going back to the complete response list when I get more data.

Patient 1 was categorized as a treatment failure by the sponsor, and I did not reassign that.

Patient 3 was categorized as a complete response, and I did not reassign that.

Patient 5 was categorized as a treatment failure, and I did not reassign that.

Patient 6 was categorized as a partial response due to the onset of new acutely inflamed lesions over the 7-day period, and I did not reassign that patient.

Patient 9 was categorized as a complete response. The lesion listings in the submission did note 13 new acutely inflamed ENL nodules appearing on day 4 in the 7-day trial, but no acutely inflamed lesions at day 7 and no fever at day 7. So, I left the patient as a complete response.

There was a little bit of confusion in my mind because there were no acute lesions and 84 resolving lesions at the first follow-up visit which was week 3, but ENL can wax and wane. So, I left that as a complete

response.

Patient 10 was categorized as a complete response, and the listing shows an endpoint temperature at day 7 of 98.8 axillary. I left that as a complete response because it's so close, even though there are temperatures in the ENL symptom assessment that are less than that coded as fevers. I left that case as a complete response.

Then again, 13 and 15 were coded as partial responses at day 7, and I left that as it is.

Patient 17 was categorized as a complete response. There were no listings for the follow-up period for that patient after the acute 7-day course, but I left that patient as a complete response because a complete response is defined at day 7.

Now, the patients that I reassigned were patient 2 who was categorized as a complete response. This patient had a fever at day 4, and there was no concomitant treatment listed in the original submission. So, that's why in my original review I expressed that I wasn't really sure whether this was a complete response or not, but I left it as a complete response, technically a complete response.

However, as the sponsor pointed out yesterday, the updated listings did show new data for paracetamol use, and the new listing does show that paracetamol was

prescribed on day 4 as an antipyretic. It's listed as antipyretic. So, this patient I recategorized as a treatment failure. Actually I think that assessment is also supported by the fact that at the day 7 endpoint that patient had persistent anorexia and malaise and edema, all three of which were coded as mild, but they were present at day 7.

Then patient 7 was categorized as a complete response by the sponsor. This patient had a temperature on day 7 of 99 in the listing in axillary temperature and no concomitant paracetamol listed in the original submission at day 3, for an axillary temperature of 101.7.

In the new listing, however, that I received paracetamol is listed for that. It's listed for 7/21, start/stop the same day, and then it's listed for 7/23. That's the date. Start/stop. The reasons noted, as an antipyretic. Those dates correspond to treatment days 5 and 7, and day 7 is the acute endpoint. So, even if that patient wasn't febrile at day 7, according to the protocol, would have been a treatment failure as the sponsor pointed out yesterday because any antipyretic use after 72 hours in this study was to be considered a treatment failure.

Then patient 8 was categorized as a complete response, and this patient had at day 7 an axillary temperature of 99 degrees, which is higher than the

baseline temperature of 98.6, for which paracetamol was listed in a concomitant medications listing. So, I reassigned that patient as a partial response because that patient's lesions resolved at day 7.

Then patient 11 was coded as a partial response because he had nine acute lesions at day 7, nine new acutely inflamed lesions at day 7. The listings for concomitant medications show that paracetamol was started on 11/25 and stopped on 11/29 as an antipyretic, and 11/29 is day 7 according to the line listings for the temperature charting. So, I reassigned that patient as a treatment failure because of new acutely inflamed lesions and temperature.

The last patient, patient 12, was coded as a partial response because the patient had 109 acutely inflamed lesions at day 7. Now, this patient started with a lot of lesions, so that is a definite decrease over the 7-day course of treatment with the thalidomide. The vital signs listing shows a day-7 temperature of 99.6, so by protocol there are acutely inflamed lesions and a temperature.

Now, the secondary endpoint listings on day 7 show that this patient also had severe anorexia and mild malaise and pain. I should point out that those systemic manifestations were not primary endpoints by protocol.

Those are secondary. So, it's just added information but it's not the primary efficacy endpoint.

The severity of this patient's case was notable, as I have in my review. There were 497 nodules, 8 pustules, a baseline fever of 100.9 with a pulse of 120, which was listed as severe fever, mild chills, moderate arthralgia, and severe malaise and anorexia. The concomitant medications listing for that patient suggests that that patient actually was on prednisone previously, 30 milligrams to 25 milligrams to 20 milligrams from 11/22 to 12/12. Then it appears that the prednisone was stopped 5 days before the baseline visit because in the protocol, patients cannot be on concomitant prednisone.

Like I said, this is draft data and so I was not able to make any comment on the patient's condition at the time of the prednisone taper or the discontinuation. But at any rate, the combination of the acute lesions and the fever at day 7 prompted me to reassign that patient as a treatment failure. Like I said, this may change when we get the complete data.

DR. McGUIRE: Fred, do you want to follow up? Is that adequate?

DR. MILLER: Yes.

DR. McGUIRE: Dr. Hashimoto?

DR. HASHIMOTO: I think that the evaluation of

skin lesions should be completely separated from other systemic manifestations, like you say complete, partial, treatment failure. It's all a mixture of the systemic fevers and pains and neuritis and then skin description.

A very strict dermatologic description should be applied in this case because this is a major part of this therapy effectiveness. Evaluations should be more dermatological.

Of course, in dermatological evaluations of drugs, we take pictures. Were there any pictures taken in this study to document improvement?

DR. O'CONNELL: Well, first of all, maybe I didn't make myself clear. The primary endpoints are fever and cutaneous lesions. The other things were secondary endpoints, and I did not reassign any patients based on those endpoints. It's just added information. In my mind I look at information like that and say is this consistent.

DR. HASHIMOTO: New lesions is not adequate to assess the effectiveness. Just to evaluate preexisting lesions. What happened to those? That's probably more important criteria of effectiveness of treatment. A new lesion may not show up for a couple of days maybe, but what happened to the old lesion? That you have to pay attention to when you evaluate, maybe documentation by picture or even biopsy.

DR. O'CONNELL: It's my understanding that photographs are archived?

VOICE: Yes, they are.

DR. O'CONNELL: Right. I haven't seen them.

DR. McGUIRE: Are there other questions for the reviewers?

(No response.)

DR. McGUIRE: I propose that we take a 15-minute break.

Wait. Who has a question? I'm sorry. I didn't see you.

DR. REA: I'd like to make a comment on the --

DR. McGUIRE: This is Dr. Rea.

DR. REA: Dr. Rea from Los Angeles.

On the subject of photography. Usually within a week's time, the formerly acutely inflamed lesions will still be photographable. There will be residual vasodilatation. There may be some increase in pigmentation. To convince you on the basis of photography that the patient had improved, photography would be very misleading. It would suggest that the drug is quite ineffective, whereas the clinical response, the absence of tenderness, the change in the color, the well-being of the patient will not be reflected in a photograph. Don't depend on photography.

DR. McGUIRE: For those of you who don't know Dr. Rea, he is one of very few experienced clinical leprologists in the United States.

Are there other comments, questions?

(No response.)

DR. McGUIRE: Can I have my 15-minute break now?

(Laughter.)

(Recess.)

DR. McGUIRE: We are reconvening.

The last few minutes before the break were directed toward questions to the primary and secondary reviewer and Dr. Wilkin. Are there other questions now? If so, we can take them; if not, we'll proceed directly to the questions. I suspect that many of the individual uncertainties about various parts of the data will come up as we discuss the questions.

Yes, Dr. Miller.

DR. MILLER: I have a question for Dr. O'Connell. Kathryn, you had mentioned or you noted a discrepancy in the reporting in one of the cases that a patient in the original report had not received Tylenol, but in the report that you received subsequently had received Tylenol. Was that a later date or was that included in that first time frame when the person received

the Tylenol?

DR. O'CONNELL: I'm not sure I understand the question.

What I received in the original submission was a listing of concomitant medications, and it had patients who had gotten concomitant medications, 01 through 09, and whatever it was on the date. Then when the new draft came in with updated information, then there was more information.

DR. MILLER: I see, but that was on those dates that were originally submitted, or not?

DR. O'CONNELL: Well, see, in the original concomitant medication listing, if I recall, I think there was only a date if there was a concomitant medication. So, it's not like every date was listed and then none.

Maybe the sponsor could address it. I think it's just more information.

DR. MILLER: I guess my question is why wasn't it listed with the original submission.

DR. O'CONNELL: Yes, see, I don't know.

DR. KOOK: When the interim analysis was submitted with the original NDA, the study was ongoing. It's a study that is monitored according to a certain frequency. Subsequent to that report, we have gone back to the site again and audited another set of case report forms

relative to the original source documents, and there were some occasions of use of paracetamol that were in the patients' medical records that had not been transcribed onto the case report forms. So, that is a limitation or a problem with submitting interim data.

DR. McGUIRE: Mr. Warren?

MR. WARREN: Correct me if I overstep protocol. Definitely before the questions, I think it would be appropriate for us to make our Thalidomide Victims Association views known, but it's not necessarily a question. So, I'm just asking for the opportunity to be recognized before you go to questions.

DR. McGUIRE: You mean apart from the public hearing?

MR. WARREN: Basically what I'd like to do is just let you know how we feel about things before you go to reading the questions, if that's possible.

DR. McGUIRE: Okay. We need to know how long will it take us to learn?

MR. WARREN: Five minutes.

DR. McGUIRE: Good.

MR. WARREN: Is that okay?

DR. McGUIRE: Yes, please.

MR. WARREN: Well, I've been listening for the last 24 hours to a lot of talk about thalidomide.

Yesterday I had a bit of a little outburst just because I couldn't be quiet any longer. But here's exactly how we feel, the Canadian Thalidomide Victims Association.

We feel it takes a lot of courage to be discussing thalidomide -- mothers, ourselves, and certainly this committee.

We feel it is very important to make our view known. We will never, ever accept a world with thalidomide in it.

However, we say that knowing that down the road there will be analogs that will have the benefits of thalidomide without the horrible side effects.

Further than that, we're forced to prefer regulation of thalidomide. And I'll make that clear. Forced. It pains us, but we have come to this conclusion, that we're forced to prefer the regulation of thalidomide because we are so much more afraid of thalidomide being available as it is today or having it relegated to a secret world controlled by so few doctors and scientists, who we won't disrespect, but we would rather see it to be a very public controlled environment.

We want people to have the opportunity to make risk-aware choices. Risk-aware choices to us mean so much more than just the birth defects. We owe a lot to those people who suffered from peripheral neuritis and who are

unsung heroes and heroines in this battle towards thalidomide. We wouldn't be here today and have been recognized as so few in number, 5,000 of us left around worldwide, if it wasn't for those persons who suffer today. We'll never know who they are because we lost track of them when the sensational story of thalidomide babies came out. So, we are concerned that as much attention be given to the side effects regarding nerve damage as is given to us in any labeling and any packaging.

We're concerned too about off-labeling. Who wouldn't be? But we believe that a regulated drug with a distribution system, which we have had some input into -- and I was quite proud to always be every morning described as a conflict of interest. It wasn't really a conflict of interest. I wanted people to know that we thalidomiders have been talking this issue from every side and every angle.

About the only thing I'll say towards Celgene at this point is it's the first time a drug company has ever given respect to thalidomiders by consulting us, and I can tell you that the victims groups around the world were shocked and surprised and await my word on that.

With us the primary goal would be education, that we should be involved. As North American thalidomiders, we can assist. We are the result of an

American drug company coming into Canada and marketing this drug and giving it to us. 95 percent of our people born with disabilities are a direct result of an American drug company.

Do we harbor any ill will? No. We come today to help you to protect the American public, and we believe that we can be effective and instrumental in that process. We believe that North Americans listen to North Americans, and we think that we can help.

Does it hurt us? Yes, it hurts. It hurts to speak about this. Who thought 40 years later that we'd be talking about thalidomide?

Do we like thalidomide? No. The words to us is poison. That's what it is. Skull, crossbones, poison. It violated our mothers.

Our mothers are the true heroines and they're the victims of this drug. We're the consequence of the drug. But as consequences of anything, of a teratogenic drug, of a monster-causing drug -- very few people probably around here know that teratogenic means monster-causing. Well, I'm not a monster but if I'm a monster, I'm in good company because we have quite a brave population around the world.

I want people to avoid pregnancy during the taking of this drug. And to be equal to that, I've always

worked in many fields where I'm part of the feminist movement and I'm proud of that. I think the responsibility has to be male and female in all forms of contraception.

We want to see the language be simple and clean. We've actually had input into the language. Not all of it was taken, but for the most part, we're feeling much better.

What we do not like are the words "avoid pregnancy" under a pregnant woman in a circle. We want "do not get pregnant." We want something strong, something clean. Thalidomide causes birth defects. Thalidomide kills babies.

I'm here to also speak for the thousands of babies we'll never know were never born.

We've had input, as I said, into the wording, into the consent. We are very concerned that there be a tracking system to be sure that people have given informed consent and that it not just be a case of reading a document at a grade 2 level. I don't even care if it's a kindergarten level. We believe that we can be most effective here perhaps through a video presentation and also through the words of doctors, but we're not convinced that doctors will give consistent warnings and that doctors are necessarily aware of all aspects of their patients.

This isn't to slam doctors. Doctors operated

on me 24 times in my life making me capable to sit here, making me capable to hear, making me capable to live and breathe.

This is just to say that we believe that perhaps some workshops for doctors and pharmacists attended and perhaps cohosted by our association with appropriate people who impress me, such as Dr. Moore, would be very useful before a doctor is certified to be able to prescribe thalidomide, should that day come.

The world is watching and the world is going to follow what the United States of America does. You are our closest neighbors and we have a lot of empathy for American TV and American idioms and all that. I probably know more about the United States of America than I do about Canada.

But our people are American victims. We're not asking you for more than the respect that you've given us and the dignity. But we're not trying to give you a victim impact statement. We have some wisdom from all of this. I've had 36 years to think about this, to reconcile it in my mind and to say, oh, my God, it's come back? I can't believe it.

The courage of my group in taking this position, where we are forced to prefer regulation, is a hard-fought courage. When we see people or meet people who've actually ingested this drug, our heart breaks.

When I heard yesterday that thalidomide takes people out of wheelchairs and I think of myself and others that were put in wheelchairs because of thalidomide, tell me we don't have the moral quandary of the century.

I am empathy and we all have empathy, because of our age, for people that suffer. No one should suffer needlessly. If thalidomide can extend life, can offer a better quality of life to people, we, those who suffer the consequences of the drug thalidomide, and the degenerations that nobody thought ask us about, we say those people should be given the opportunity to make a risk-aware choice, but knowing all of the side effects.

I think it should be mandatory, any distribution system that comes down. We're very clear on the fact that we believe that while we may have one great drug company that comes along or even two great companies that come along, when thalidomide is more widely licensed by other companies, we can't necessarily guarantee that everybody is going to follow that kind of system, should you license the drug.

And what of us? We who deteriorate physically today are sad. We're somber. We're resolute in the fact that we will be there. We will be watching. We will advocate for what we believe to be the first thalidomide baby that will come along.

But in our lives, we've been in the medical system so often and our parents have been forced to make hard decisions in consulting with doctors. And I'm a Star Trek fan, so I'm going to actually give you a really good analysis. Sometimes the needs of the many outweigh the needs of the few or the one. And if you feel in your own minds that you can speak to that as medical professionals to a child who may be born with thalidomide deformities and look him in the eye and say, and this is the wonderful thing that happened because we put thalidomide on the market and this is the wonderful thing that happened because 5 to 10 years from now thalidomide is banned as a substance because we found something to replace it, but in that in-between time when you were born, you weren't sacrificed to the slaughter. You became a hero or heroine to the cause of helping to alleviate suffering.

In some ways, some small ways -- and it's so difficult to say because of so many that have died or were never born -- maybe, maybe the second go-around may do some good. So, I just want to end on the note, we will never accept a world with thalidomide in it. We insist that you dedicate resources to researching an analog with the benefits of thalidomide but without the harmful side effects. We deserve to be recognized for what we've gone through, but more recognition should be given to our

mothers and I think they should be symbolized. I hope our mothers will join us in this education process.

And we are afraid of thalidomide the way it's available. We've seen it on the Internet. If you have a U.S. address, you can probably get it. You know, hide it in a jacket as you're coming across the border from Mexico. How do we know what's being told about this drug? How do we know who's being protected? Isn't one thalidomide baby born out of ignorance worse than one thalidomide baby being born out of justice and a good attempt to regulate and control the distribution process?

And isn't it something amazing that we're sitting here today and that I'm able to address you when we weren't supposed to live past the first 5 years, and then the first 10 years, and the next 20 years, and the next 30 years? We are only the 40 percent that survive from live birth. We don't know what we herald. I want to make that point really clear. Our deaths are in an unknown quantity. Nobody knows how long we will live until we all die together because we are one group together and we're a family.

So, our family has just told you what our family needs to tell you. We trust you. We trust you that you're wise men and women and that from this process on, it will be even wiser. But we insist and we know, even if

it's not agreed to, that we will be here and we will be watching and we will be helping whenever we're asked.

Thank you.

DR. McGUIRE: Thank you, Mr. Warren.

(Applause.)

DR. McGUIRE: Thank you for taking the time to put that together. It's very important for the agency and for the committee and for the sponsor to have heard that. We appreciate it.

I would like to go on with the questions and let the questions provoke discussion.

First, you must understand that the advisory committee does not generate these questions. These questions are generated to challenge us and to bring out the best in our judgment, and so we'll see.

But first I'd like to say that I spend most of my time considering dilemmas. I really like the choice between something good and something bad because that's not a dilemma. Then the real dilemma is choosing between something good and something else good. That's the kind of dilemma I like. But the worst dilemma is trying to make a choice between something bad and something bad and you decide which is not quite so bad as the other bad. That's enough of that.

Number 1, has the efficacy of Celgene's

thalidomide in the treatment of the systemic erythema nodosum leprosum, ENL, syndrome or any subset of ENL, such as cutaneous ENL, been demonstrated?

Now, I know that we have a word from the sponsor about the analysis of safety data and we can get into that in a minute, but I'd like for the committee to start with this issue.

By the way, these questions can be fragmented. It has been my experience that the agency sometimes consolidates a question that has many different pieces, and so if you want to take a piece out of one of these questions and address it, that's perfectly acceptable.

Dr. Bergfeld.

DR. BERGFELD: I think if we look solely at the question about efficacy here and we look at the various percentages of efficacy that have been presented to the committee -- and it seems to me in my mind it ranges from 40 percent up to 100 percent -- that in the face of looking at thalidomide as a therapeutic help in ENL, we might consider those to be therapeutically helpful.

I think that the problem that we have today is the premature presentation of information that has not been cleaned up and that there is an incomplete study that might be exceedingly helpful.

Then the larger issue perhaps is toxicology

issues.

But I would ask the FDA when you're looking at efficacy, what is the percent of response that you demand, the range of percent of response that you demand of any drug that is considered?

DR. WOODCOCK: Yes. I'd like to answer that.

There were a number of points made. We talked about this a little bit yesterday, about the quality of the database, and also you're raising really a new question about the meaning of effectiveness in this context.

To reiterate about the database, there are at least three or four kinds of data that you're being asked to evaluate.

You're being asked to evaluate placebo-controlled literature reports. The agency has sometimes approved efficacy supplements of drugs based on literature reports alone, when there were enough of them and they were robust enough and independent enough.

You're looking at retrospective data analyses which are basically historically controlled data. As we discussed yesterday, the reliance upon historically controlled data is dependent on the expert assessment of the natural history of the disease and how reliably you can infer from the observed response and compare it to the historical response. For example, in cancer we do that

routinely, and response rates to different antitumor agents are accepted because of the known low historical response rate. So, for example, in many tumors the oncologists have decided that around a 20 percent response rate is what you might observe in the background and responses above that in the historically controlled trial are indicative of response, and that varies with tumor type and so forth. That's not a generalization but it's an example.

We're also seeing -- and you've alluded to this as somewhat of a problem -- a preliminary analysis of a dose-controlled study. It is a controlled study that is ongoing. Its primary endpoint is fever and cutaneous lesions apparently, but in this analysis for the purposes of today, you're really looking at again historically controlled data. You're looking at the response rate in that 20 patients or whatever, compared to what you would have expected a response in those patients had they been untreated for cutaneous, for fever, and so forth.

FDA can accept historically controlled data, as I said, but it really depends on how reliable you feel the inference is that can be drawn.

Now, as far as the effect size, which is what you're talking about, we usually define effectiveness as meaning a beneficial effect on the patient. We don't really take size into account unless the size is so small

that we have doubt that it's a clinically meaningful effect, if you follow me. So, many of our surrogate endpoints, such as cholesterol lowering and antihypertensive effect and so on -- drugs are approved on those because we believe that will reliably predict a beneficial effect on the patient. The size of that effect really isn't known in many cases.

For other products, though, for example in my area of expertise, in rheumatology, usually placebo or active controlled trials are done, and we look for a statistical difference of a beneficial effect on the patient. The size of that effect isn't taken into account. You merely have to show the effect.

Does that answer your question or not?

DR. BERGFELD: Well, if I'm interpreting what you say, it's that it has to be a statistically evident effect.

DR. WOODCOCK: Only in a trial that is set up as a randomized controlled trial, that would be the kind of endpoint.

DR. BERGFELD: So, backing up then, what you really said, it has to show effect no matter what the range of effect is.

DR. WOODCOCK: That's right.

DR. BERGFELD: It has to be greater than what

is perceived either as historical or placebo-controlled trials.

DR. WOODCOCK: And then what is done is the risks of the drug in that condition are evaluated separately and an attempt to quantitate them in as best a fashion as possible is done, given whatever the data set is, and then a risk-benefit analysis is conducted to see, if with the projected effectiveness of the drug and the known estimated risks, do the benefits outweigh the risks in that case.

DR. BERGFELD: But the question we have been asked has nothing to do with risk. It has only to do with efficacy.

DR. WOODCOCK: That's question 3.

DR. BERGFELD: Yes, I know. But I'm trying to answer question 1 because what has been presented is a mixed bag of data.

DR. WOODCOCK: That's correct.

DR. BERGFELD: And it seems that there is a range no matter what the control or pseudo-control was, the historical control, but there is a suggested efficacy here.

DR. WOODCOCK: Well, we're asking your opinion about whether you can -- what your confidence is that the data, given their limitations, show a clinically significant effect, not huge effect or whatever, an effect

that would be beneficial to patients.

DR. BERGFELD: Well, I will say that my opinion is this data does demonstrate that.

DR. McGUIRE: Are there other comments? Yes, Dr. Mathews.

DR. MATHEWS: I'd like to comment on a slight reformulation of the question addressing not Celgene's product but thalidomide as a generic entity in this syndrome.

As I've read the agency's review and the sponsor's review, I was struck by a contrast in paradigms. I must say I, on balance, come down on this issue not with the regulatory viewpoint, but more as I would consider an informed clinician who is used to reading scientific literature in medicine. I find that I cannot concur with the paradigm that this body of literature, which has been summarized, is comparable to the studies that Dr. Wilkin referred to in his comments, for example, the internal mammary ligation syndrome, the insulin shock therapy approach, because there are controlled clinical trials that we were asked to look at the reports in peer-reviewed medical literature. What the agency had to do, as I understand because of the regulatory requirements, was to reconstruct, as best you could, actual data sets from source documents which were no longer obtainable.

But as I look at the controlled clinical trials and gave most weight to the Hastings paper and to the World Health Organization trial, which wasn't a trial from which you had access to the source documents, I was convinced that there is a beneficial effect, at least on fever and skin lesions by whatever formulation of thalidomide was used in those two trials.

Supplement that by the fact that the people who take care of patients with leprosy are an elite group of clinicians who have done this for years -- Dr. Rea, for example, was a professor of mine in medical school over 20 years ago and lectured us on leprosy, and that was the last time I actually saw a patient with leprosy. But I have enormous respect for the very careful clinical observations of these investigators over the years, not that I give them the same weight as a clinical trial because they're subject to bias like any of us are, but there is a consistency of effect.

So, on balance, I would just summarize my impression that, yes, I don't think personally that a placebo-controlled trial is required to show that thalidomide works for skin manifestations and fever.

DR. McGUIRE: Thank you very much.

Dr. Miller.

DR. MILLER: I think we have a body of data and

we've heard from the experts about their results and their observations over the years, and it clearly appears that thalidomide is effective.

The question here is the meaningful efficacy of Celgene's thalidomide. I think that raises a question because here we are in 1997 and it's time to do a study and I think we can do a good study, but we have here a protocol which was aimed I think at 30 patients. When we came into this session, we had observation on 9 of those 30 patients, and then we picked up an additional 8 patients and just heard the data on those.

So, it's very difficult to come to any conclusions, and still at the same time, we've got to demand that we have this data and that we have good data. The definition appears to have been truncated a bit and we're limited now to cutaneous lesions, and if it is limited to cutaneous lesions in our definition, well, then we certainly should be able to observe those very well and come up with an accurate assessment.

But we can't just do a 1-week or a 6-week. We need some follow-up because in the presentations yesterday, it was apparent that most of these patients who have been put on thalidomide remain on thalidomide for long periods of time. Again, then we have to define the subsets who really need thalidomide at the outset, and if you don't

need it, well, then what are the other modalities that could be used?

So, I think from this study we do need to get some meaningful data, but we just don't have enough patient data at this time.

DR. McGUIRE: Ms. Cohen.

MS. COHEN: Dr. Mathews, did you say or did someone say if they left the word "Celgene" out, it would make a difference? I thought someone had said that.

DR. MATHEWS: I think there are two separable questions. One asks you to review the historical body of literature and make a judgment about is there evidence that some form of thalidomide is effective in this syndrome. The specific question facing the committee assumes I think the answer to that previous question because that is a major body of the evidence that is brought forward to support the specific application of Celgene.

I agree with Dr. Miller that because of the prematurity of the current ongoing clinical trial data set that I cannot answer in the affirmative that Celgene's product is effective in a regulatory context. If at a committee meeting, discussions have to take place about where you classify individual patients as responders or nonresponders, there's some problem.

MS. COHEN: I like the nuance of what I thought

you suggested and I have to say that I would go along -- if it's possible to remove the name Celgene and do it. I think it takes a whole different --

DR. McGUIRE: Dr. Hashimoto.

DR. HASHIMOTO: Well, I assume this is a kind of helpful drug by hearing from all the experts, and that's the extent I can understand the situation.

As far as data is concerned, the database is very confusing, and I am not 100 percent convinced that this is done in a legitimate way in today's standards.

So, also there's no reliable dermatological descriptions in this protocol. It just says new lesions didn't show up, but that is not today's drug studying dermatological disease. It's really not an acceptable description.

So, it should be more wide-based and long-range dermatological evaluation which is one of the major components of this drug effects. So, the study should be redesigned and dermatologists should join the group and descriptive portion -- as I said, photography is probably required. You can tell the closure of the ulcer easily by a picture. There must be some documentation. That's my opinion.

DR. McGUIRE: Thanks, Ken.

Dr. Orkin?

DR. ORKIN: In reviewing this material, there are three words that come to mind that have been already alluded to: promising, confusing, and premature.

DR. McGUIRE: Did you find anything that you liked?

(Laughter.)

DR. ORKIN: Promising.

DR. McGUIRE: Promising, okay.

If I can tell you what I've been hearing for the last 10 minutes, everyone sitting around the table who has clinical experience is inevitably influenced very heavily by the opinions and the experience of doctors like Gelber and Dr. Rea and Dr. Yoder. They clearly have more experience in six weeks than any of us would have in six years. It is inevitable that that kind of experience is very influential at least on the clinicians.

There is a problem and the problem was that a decision was made to review old data, data obtained from patients who were treated with thalidomide from various sources, and an incomplete data set doesn't quite cover it. I think it was cruel and unusual punishment for the sponsor to have to go back and sort out those data and try to analyze them in an orderly fashion.

We'll do a fast-forward to the present Philippine study which, although Dr. Wilkin observes does

not have a placebo in it, I think it's very difficult to have a placebo arm in this kind of study. So, we have a two dosage range study that's going on with the proposed goal of treating 30 patients, and now we've seen data on I think 18 or 20. I think that fits your observation. Those are very promising studies.

Then the problem is I think none of us was prepared yesterday or today to sit and analyze individual cases, that is, whether case 11 belongs in this category and case 9 belongs in this category and the sponsor thinks that case 12 belongs here. Those are not the kind of clinical data that are powerful in moving you into approval or disapproval. So, there is a problem with the sample size.

Dr. Wilkin, how have I misquoted you?

DR. WILKIN: No. You may well have quoted me verbally, but I think in my review I think what I had was an active control could be performed for the E-003/P. It could have a sedative, for example, in it. It could also have prednisone. Prednisone for a week shouldn't be a problem. It might have instead of prednisone, perhaps one of the more potent nonsteroidal anti-inflammatory agents, but an active control.

DR. McGUIRE: Eva?

DR. SIMMONS-O'BRIEN: I would just like to say

a few comments.

I think to answer the question, I think Celgene's thalidomide has shown to be efficacious in some of these patients. However, I think in 1997 we would like to see this medication, if it's used in a condition such as ENL where it has been shown to be effective over the past 20 some odd years or longer, that Celgene provides us with a model study using clearly predetermined objective measurements of clinical response comparing thalidomide to gold standards of treatment of ENL, prednisone and/or dapsone, looking at toxicities in both of those arms, looking at mechanisms of action.

Just to go back to yesterday when Dr. Thomas was saying that the educational package was not specifically directed towards ENL because he was making the point that one day in the future this is a medication that will be used for off-label indications or other indications, that they wanted to go ahead and have some uniformity to make a really gold standard of how physicians, patients, and the public should be educated.

Well, I would throw the challenge back to them saying that this study on ENL in the Philippines should be the gold standard by which other studies are done for other NDAs. And that's what I don't see.

DR. McGUIRE: Yes, Dr. Mathews.

DR. MATHEWS: One of the implications of an active control arm is clearly on sample size. I would suspect if prednisone were the active control, you would need a much larger sample size, and I wonder whether you would be looking at an equivalence trial in the short term and not on a superiority trial. I don't know if there are enough patients to do an equivalence trial in any single site.

DR. LUMPKIN: Just on a procedural thing there, as Janet was saying a little while ago, there is not a comparative efficacy standard for approval procedures in this country. What has to be shown is that the product itself, that's the object of the review, indeed offers something of clinical benefit to the patient. I think you're absolutely right.

As Janet talked about coming out of her experience in rheumatology, my experience is in anti-infectives where we don't do placebo-controlled trials for obvious ethical reasons there.

The point that we're trying to make I think in active controlled trials is not is one superior over the other or is one equivalent to the other. Those are nice things to know and there are clearly people within the health care world who want to know those things, but in trying to determine is the product under review effective,

what that trial design offers us is a way to try to deal with some inherent biases that would be in an uncontrolled trial, albeit as we've all said here today, an active controlled trial has its own problems with biases depending on where you're going.

I think you do bring up a very good point. We found that in the anti-infective world, where we have a lot of people who have the common infections, those trials sizes, when you're trying to get to statistically significant superiorities or statistically significant equivalence determinations, can be quite large. That's a very big problem when we're going into orphan indications like we're talking about here.

I think in that situation we would not have the expectation that one was showing something statistically because of the realities of the disease entity being treated. We would use a trial design to eliminate bias so that the observations that you make on the product under review can be believed to be more robust so that you have to make a kind of a scientifically clinically relevant decision of has this product offered anything of value to the patient.

So, I don't want you to think that there's some magic in a regulatory decision versus a scientific decision. These are all scientific decisions. Ours have

regulatory implications but it's still a scientific decision. It's a clinically relevant decision and that's what we need input on.

DR. McGUIRE: Dr. Gelber, did you want to speak to the issue of efficacy? Let's leave toxicity out right now.

DR. GELBER: First of all, I want to thank the clinicians for believing us. I rather thought that our opinions, no matter how long we've been in the field and how many patients we've seen, you might conceive that we've been duped over a prolonged period of time.

Actually I understand proof, as well as most of you do, and I understand controlled clinical trials.

First of all, let me say my experience, you already know, has been over nearly 30 years. I was in on the IND from its initiation. I respect the considered reviewers who are looking as academics at a body of data that I might add I reviewed for Celgene and signed the reports that the FDA received. I looked over a lot of literature and, frankly, was surprised that there was so much. When I saw the literature, I saw the very same flaws that all of you saw, and yet I think I was impressed with the body of the data and the unanimity of the opinion.

Clinical trials in ENL are very difficult. I am infections disease person and not a dermatologist. I'd

hate to see what penicillin would do here at this meeting because one can't do those trials either. But that in a sense is an aside.

Clinical trials in ENL are very difficult. First of all, the endpoints in almost all of the trials vary from place to place. This is not a syndrome where we have a readily available number like an SGOT or a blood pressure or things that can be easily measured. A lot of it is patient response and a lot of it is fairly subjective. It is not easy to do a careful controlled clinical trial.

Yet, I think there have been attempts and I think most of the attempts have been honest ones and I think the results have been uniformly similar.

Furthermore, when I write textbooks on this, I say ENL is a systemic disease and probably it's a vasculitis, and I suspect that most of the manifestations are really more a function of where the immune complexes land than anything else. My belief would be that if thalidomide is effective against skin lesions and fever, it's likely to be effective against the other manifestations, which is certainly my own and other's clinical experience.

Yet, when you look for the data on that, it really is rather hard to come by in anything that

approaches controlled clinical trials, but there are an awful lot of large open-label trials that attest to its use. And the reason why it's hard is that skin lesions and fever are far and away the most common manifestations. So, it's hard to do studies.

I think the next-to-the-last point is that I think that a lot has been placed on the Celgene product. I think it has been fairly clear, at least in steady state, that this is equivalent to at least other historical thalidomides, and I think it's fair to extrapolate that this product at least is equivalent in its bioavailability. Hence, I think it's fair to extrapolate that one needn't create a massive database on the Celgene product itself.

The last thing I want to square -- and I think this is important. You've seen a lot of different response data analyses from Celgene itself, from my reviews of the literature, and from independent and carefully considered considerations. I think these are largely explainable by endpoint decisions and how one views the natural history of the disease.

Dr. O'Connell, I think you felt that one patient got put down in the lower response category because there were ulcers present or ulceration occurred during the course. Well, thalidomide does not affect the natural course of individual lesions, nor does anything. Really

what it does is prevent new lesions from occurring.

I think, Dr. Weintraub, in your analysis of the L.A. data, you found that there were treatment failures that occurred that we would have called successes or at least partial successes because there were some skin lesions. So, your endpoint was a little more stringent than would have been called failures by the criteria that were used.

So, I think I just wanted to share. I've had some diverse views here on diverse issues, but I did want to share some of these opinions and leave you with the view that I appreciate your considered thought. Having spent a lot of time on these reports and a lot of time with these patients, I'm fully convinced that the massive database in the literature and the clinical experience there leaves little doubt in my mind that this drug is effective in all manifestations of erythema nodosum leprosum.

DR. McGUIRE: Thank you, Dr. Gelber. The committee appreciates the clinical experience that you bring to this and also your willingness to analyze the data.

Are there other questions from the committee? Yes, Eva.

DR. SIMMONS-O'BRIEN: Not that there's a question but just to further take up that point. It is

very difficult to look at objective measurements in a small population and in skin, but it can be done. It's timely and it's very expensive, but just not photographs as the only mechanism. Photographs are helpful. Reevaluating the tissue histologically can be helpful. Having the patients fill out a survey as to how they consider or how their symptoms are doing in terms of burning, swelling, induration, redness. There are also instruments out available now that can measure the erythema as well as the melanin index in a lesion.

So, there are a whole bunch of things that can be done and then looked at to see if that also correlates with a good response, a complete response, or a partial response, but yet they are very expensive and they take a lot of time, but it can be done.

DR. McGUIRE: Yes, Joel. Dr. Mindel.

DR. MINDEL: I'd like to disagree with Dr. Lumpkin a little bit in that he seems to feel that this is a scientific and a regulatory meshing. But for me, this is a divergence of scientific and regulatory decisions. I have a faith that the drug is effective, but scientifically I don't believe the data support that it's effective. This is the first discussion of a drug where nobody has mentioned .05 probability. Statistics have not come into this discussion at all. If this weren't an orphan drug, it

would not have been at this level of a meeting.

I think we really have to throw the weight back to the FDA that it's going to be an act of faith to some extent and the reports and the literature and the experts who feel that it's effective and the faith maybe of the people around the table that's going to make you approve or disapprove the drug.

DR. WOODCOCK: Yes. I think Mack and I both would like to respond to that perhaps.

There are different ways to arrive at a level of certainty and we use different methods when prevalence in the population is very small or for other reasons we cannot do randomized trials. Oncology is a good example. For the first approval of oncology agents and for many other types of treatments, randomized trials often cannot be done.

That doesn't mean, though, it isn't a scientific judgment based on the natural history of the disease, the robustness of the data, the multiplicity of observations that have been made, the independence of observations. These are not simply specific to this discussion. These are things that we have laid out and discussed publicly as far as the bases for decision making when randomized controlled trials are not available.

DR. McGUIRE: I'm getting close to asking for a

vote on the first question, but I'm going to modify the first question very slightly. Mike, I'm not going to do anything bad to it. I'm just going to leave a part of the sentence off.

Has the efficacy of Celgene's thalidomide in the treatment of systemic erythema nodosum leprosum or any subset of ENL, such as cutaneous ENL, been demonstrated? What I'd like to do is put a period after "syndrome," and then if we want to consider efficacy for subset, we can do that as a second question.

So, the question now reads, has the efficacy of Celgene's thalidomide -- this is not Chemie Gruenenthal's thalidomide, and it's not Tortuga's thalidomide. Has the efficacy of Celgene's thalidomide in the treatment of systemic erythema nodosum leprosum syndrome been demonstrated?

DR. WOODCOCK: Could I just add one more clarification?

DR. McGUIRE: Dr. Woodcock.

DR. WOODCOCK: I apologize for interrupting the flow.

But as far as Celgene's thalidomide versus other thalidomides, we would like the committee to tell us what they think about the efficacy of thalidomide.

Dr. Weintraub and Dr. Lumpkin and I don't agree

with the statement that was made that formal bridging bioequivalence data should be obtained to the other formulations that were used in the past. The reason for that is those were not defined formulations, and it isn't at all clear that even if a number of those were tested, that you would know what the dose that was received in the historical database for any specific patient who responded was and what the absorbed dose was.

Therefore, we are interested in the question of whether the committee believes that thalidomide itself is effective and the questions about Celgene's thalidomide is effective relate really to dose and safety at the dose.

DR. McGUIRE: So, you're suggesting that we amend the question? I think it's your question. It's not my question.

DR. WOODCOCK: Well, we would like to have the answer to that question as well is what I'm saying. It might be useful if you entertain that question first, but it might not. I would say it's up to you.

DR. McGUIRE: Mrs. Cohen.

MS. COHEN: Could you make it a two-part question, a little different? Has the efficacy of the data on thalidomide, because it is a lot of data there that doesn't come from Celgene. I think if you use the word Celgene and nothing else -- I used to draft my own cease

and desist agreements. I'm not a lawyer, but I've done a lot of it. I'm a little uncomfortable with it because as we go on and we vote, it kind of ties us into Celgene, and maybe we shouldn't be in the other things we're going to say. So, I don't know if you can divide it into two questions: the data, one; Celgene for another.

DR. McGUIRE: Well, we have several kinds of data. We have anecdotal data. We have clinical data. We have historic data. We have Bob Hastings' data. We have current data from a pretty clean study going on in the Philippines. And the question is where do you put your bets.

The other issue that comes up is that Dr. Woodcock has suggested that we consider not just Celgene thalidomide, but global thalidomide, and we can do that as a separate issue.

I think what I would like to do now, Susan, if you'll let me, is --

MS. COHEN: It's a free country.

(Laughter.)

DR. McGUIRE: -- to deal with Celgene. Has the efficacy of Celgene's thalidomide in the treatment of systemic erythema nodosum leprosum, ENL, syndrome been demonstrated?

DR. BERGFELD: Can I ask for clarification? At

this point in time or our projected feelings about the future reporting of a study that's under way? We're prematurely making decision on a current study because the only study they have is that Philippine study.

DR. McGUIRE: Wilma, you know, you got me there. I didn't write this question.

MS. COHEN: Well, that was my point.

DR. McGUIRE: Fred, help me out here.

DR. MILLER: I think the adjective "meaningful" is important here. Again, I guess I'm reiterating what I said before.

But first of all, this study is not unblinded yet and we don't know if 100 milligrams or 300 milligrams is the appropriate dose or some other dose. And we have too few patients to really make a decision on. I think as Eva said, we have the opportunity to have a study here from which you can get some really good data, and now is the time to do it. Until we see all 30 patients and the data from these 30 patients, I don't think we can say, yes, this is truly meaningfully efficacious in the treatment of ENL.

DR. BERGFELD: I want to comment again. I have never had a committee vote on a study under way as to whether it was going to have an outcome that was beneficial or not. So, I refuse to vote on this question as stated.

DR. WEINTRAUB: Excuse me. Can I make a point

here?

This study was never intended to be one of the ones upon which this decision would be made. It in fact was designed as a phase IV study, although it was begun now. It was to be completed after the approval -- if the drug were to be approved, it would be continued on and finished after the approval process. So, it's not that it should be such a major part of it. If you want to back away from it, that would be acceptable as well, and just look at the database without the Philippine data.

Actually it's coming in in piecemeal, but we have been required to do that both by the fact that this is a priority drug and reviewed very rapidly and also by the fact that we wanted to get all the information we could for the committee to look at.

And the other thing is that this, remember, is it is an efficacy trial, but it's also a dose-ranging trial. That's one of the things we want to look at in this case, is which dose, what dose, how will people respond to different doses.

DR. McGUIRE: But the question we're being asked is one of efficacy, and Dr. Bergfeld's point is pretty straightforward, which is that you are putting us in a position of advising you on the basis of a partial study, a study with few patients in it. To be sure, it's a blind

study and it's a very good study, but it hasn't been broken yet.

I'm coming back to the same question over and over. Do you want us to consider the totality of thalidomide experience in ENL and forget about the Celgene?

DR. WOODCOCK: We are not asking you to say has the efficacy of Celgene's thalidomide -- only in trials that have used Celgene's thalidomide. Now, we recognize that that issue relates to dose, dose response, and safety as far as what the dose of that product is, but we're asking about the efficacy of thalidomide.

DR. McGUIRE: It's the easiest thing in the world for me to mark out Celgene. Okay.

Has the efficacy of thalidomide in the treatment of systemic erythema nodosum leprosum syndrome been demonstrated?

I think the only way to do this is to walk around the table and vote. Fred, are you prepared to vote?

DR. MILLER: Again, we've heard from the experts, and I think that it is effective. But we've also heard the caveats about the published studies on thalidomide and the reasons for those caveats. But, yes, it does appear to be an effective drug.

At what point do you use the drug? Are there less teratogenic drugs that can be used for the same

entity? I think there are big questions.

The thing that bothers me the most about this is that this is a teratogen which has caused significant problems and now we're looking at it before the one study that might be available is not even finished, and it just does not seem to be consistent.

But I think yes, thalidomide is --

DR. McGUIRE: That's a very long yes.

DR. MILLER: Yes.

DR. McGUIRE: Dr. Hashimoto.

DR. HASHIMOTO: Well, I think it depends on what you define the syndrome. I think fever probably evaluated and probably effective to control fever. Skin lesions. I heard many experts say it works, so I think it works. But when you talk about orchitis, uveitis, neuritis, there's no evaluable quantity of data there, so I have no idea what it is. I should say in a selected area, it's effective.

DR. McGUIRE: So, you would vote yes if this were cutaneous.

DR. HASHIMOTO: Yes, cutaneous and maybe fever.

DR. McGUIRE: Cutaneous and fever.

Mrs. Cohen.

MS. COHEN: Well, you were trying to subdue me before, so I'm going to try and be subdued, but I'm not

sure I can.

Efficacy is a very interesting word in terms of definition. Has the efficacy of thalidomide and possibly other drugs -- I mean, because we don't know enough. But if you want me to vote yes, I'll vote yes.

(Laughter.)

MS. COHEN: But I'm not thrilled, I can tell you. When I hear that the lesions can go in 48 hours, that really kind of says something to me.

I feel the FDA wants some direction on how we feel about thalidomide as one possibility, and it isn't the only possibility I suspect. This is really focusing in on thalidomide and nothing else, and that's what concerns me.

The questions are very difficult and it's hard to draft them and it's to answer them. Sometimes I think we ought to have input into the questions too.

DR. McGUIRE: Well, Susan, in the first place, I'm not at all persuaded that if you thought I really wanted you to vote yes, you'd vote yes.

(Laughter.)

MS. COHEN: That's why we get along. He understands me very well. And we do need a little levity once in a while, if you'll forgive me.

DR. McGUIRE: So, are you voting yes?

MS. COHEN: May I think about it a little bit

more, please, and come back?

DR. McGUIRE: You sure can.

Dr. Kilpatrick.

DR. KILPATRICK: In short, yes.

DR. McGUIRE: Dr. Simmons-O'Brien.

DR. SIMMONS-O'BRIEN: Yes, and if you review the literature, you'll see it.

DR. McGUIRE: Dr. McGuire, yes.

Dr. Bergfeld.

DR. BERGFELD: Yes.

DR. McGUIRE: Dr. Orkin.

DR. ORKIN: Yes, for skin and fever.

DR. McGUIRE: Dr. Mindel.

DR. MINDEL: No.

DR. McGUIRE: Dr. Mathews.

DR. MATHEWS: Yes, for skin and fever.

DR. McGUIRE: So, in fact, we put that question back together after I took it apart, and what we did was eliminate -- I believe it's my sense of what the advisory committee wants is that we're voting yes on efficacy for skin and fever, and we don't know about the other pieces of it.

MS. COHEN: That makes me more comfortable.

DR. McGUIRE: Everyone is going with that?

MS. COHEN: Yes.

DR. McGUIRE: Susan, would you care --

MS. COHEN: Yes, sir. As long as it's skin and fever, I'll be more comfortable.

DR. McGUIRE: Okay.

The second question. Dr. Woodcock -- oh, I'm sorry. Madeleine Duvic's vote?

DR. BERGFELD: She was yes.

DR. McGUIRE: Is yes.

Dr. Woodcock, do you want to delete Celgene from question 2?

DR. WOODCOCK: Yes.

DR. McGUIRE: Has the safety of Celgene's thalidomide been described in the treatment of systemic ENL syndrome or any subset of ENL such as cutaneous ENL been adequately described? Okay, I didn't write that question either.

I think the sense of the question is, has the safety of thalidomide been adequately described in systemic ENL or any subset of ENL, such as cutaneous?

DR. LUMPKIN: Joe, just for clarification on that. You know, as people obviously see, when we get to question 3, it's the basic risk-benefit there. We're not asking people here to say is this drug safe. We've spent a day and a half talking about all the various concerns people have.

What this question is asking, has the safety profile been adequately characterized so that when we get to number 3, you've got a premise upon which to do a benefit-risk assessment. That's really what this question number 2 is getting to.

DR. McGUIRE: Well, before we address that question, I would like to ask Dr. Crawford his views on that because as I sat here in November and listened to the data on neuropathy, axonopathy, it seems to me there were different measures in different studies and there were different results in different studies. I was left without a clear view of what the neurological toxicity is.

DR. CRAWFORD: I don't think the neurotoxicity has been amply demonstrated.

I support Dr. Miller's point, that ENL is chronic, it's recurrent, it lasts for years, and thalidomide has been given for many months or years.

As I tried to point out, the toxicity we know for a fact, in well-documented studies in non-leprosy disorders, the frequency of thalidomide neuropathy is at least 21 percent, and as somebody has pointed out, in one British study it may reach 50 percent. That is based on electrophysiological studies which have not been performed on leprosy patients.

Now, experienced leprologists have stated they

have not observed this neuropathy in leprosy patients. We really have to ask the question, why is this difference occurring, a difference of between lower than 1 percent and upwards of 21 percent?

One answer is I noted from the Hansen's Disease Center form, that the information on that form showed details of the classification of leprosy, but there was nothing about the clinical examination of the peripheral nervous system. Now, this is not a difficult thing to do. You need a pen, a piece of cotton, a reflex hammer. That should be recorded at the very start before thalidomide is administered, and that will give you a baseline as to whether the drug is safe or not.

Now, we're told from the leprologists they carry out careful sensory codings, but we haven't seen any clinical data on that.

So, I think in summary that the evidence suggests that thalidomide neuropathy has not been excluded.

I'm also very concerned about the advocates of thalidomide, including Dr. Gelber, when they're writing about this in textbooks -- I think he has written in Mandel's Infectious Disease -- he doesn't mention thalidomide neuropathy as a side effect, and I think that's a serious omission.

DR. McGUIRE: Dr. Simmons-O'Brien, would you

make a comment about some of the literature you've looked at with neuropathy?

DR. SIMMONS-O'BRIEN: Yes, and I have to say I am not a neurologist and I wish sometimes I had paid more attention to neurology in medical school now in reviewing some of this.

But as a dermatologist in reviewing literature and being concerned about some of the patients that I used thalidomide in compassionately -- and that thalidomide has not been obtained from Celgene, I'll say that -- I think that in the ENL patients specifically -- and that's what we're talking about -- the literature -- and I agree with Dr. Crawford -- does not look like the thalidomide neuropathy as it is characterized was looked at in the past. And it doesn't seem like from Celgene's report that it is being looked at today in a very standardized way using a standardized history, neurologic examination, looking at sensory nerve action potentials, and the median in sural nerves, looking at somatosensory VOC potentials, and looking at quantitative sensory testing to measure vibration and temperature, all of which has shown to be helpful in further elucidating a toxic neuropathy as demonstrated by Dr. David Cornblath, who was here yesterday. I think that it must be done prior to a patient ever beginning the medication and it should be done at

systematic intervals.

So, I don't know that ENL patients do not get thalidomide-induced neuropathy. It seems to me that it has not thus far been looked for.

DR. McGUIRE: Is there more discussion on that point? Yes?

DR. MATHEWS: If I recall correctly, at the November meeting there was a discussion about whether a clinical examination was sufficient once a drug is licensed or made available for clinical practice to detect neuropathy due to thalidomide or any other medication that has neurotoxicity, or should electrophysiologic studies be required. I think, if I recall, it was Dr. Cornblath's comment at that time that careful clinical examination was likely to be adequate to detect reversible neuropathy.

In the data that has been discussed so far yesterday on reversibility of this entity, the neuropathy, I don't recall hearing any data that detecting it when the nerve action potential decreased by any specified amount was any more likely to be reversible than discontinuing the medication at the first sign of paresthesias, for example.

It's a big difference to require nerve action potentials be measured in a clinical trial setting versus stating that that has to be part of the monitoring of the drug whenever it's used in any clinical care setting

because it's simply not available in many contexts. So, I think we have to grapple with that issue.

DR. McGUIRE: That's my recollection of Dr. Cornblath's testimony.

Yes, Eva.

DR. SIMMONS-O'BRIEN: I think the problem gets into reversibility of neuropathy and reversibility of symptoms. I was not at that meeting and you did not hear any data yesterday to suggest that. However, in my experience, clinical evidence has shown that there seems to be a window that you can actually reverse the neuropathy if you are using all those measurements and there is a time when the neuropathy most likely is still present based on depression of those synaptic responses. However, the patient off of medication is no longer symptomatic or the patient on lower dose medication is no longer symptomatic.

So, it's a very gray area. It's a very difficult area but it's one that we need, to the best of our ability, to try to understand and look at. The benefit will be that hopefully we'll have a better understanding of neuropathies in general.

DR. McGUIRE: The question is has the safety of thalidomide in the treatment of systemic ENL or any subset of ENL been adequately described. What I'm hearing is that we need to fill in some data in the neurologic exam and

perhaps make predictive observations.

Dr. Bergfeld.

DR. BERGFELD: Well, I'd like to respond to that question as well. I think that the safety information as to where we should be looking for the risk areas has been adequately described. We've heard about the embryo toxicity, the neuropathy. We haven't mentioned the hematopoietic changes that occur in some individuals. But I think that all of the studies paint sort of the same picture, and so we know where our issue areas are.

So, I would answer that question yes.

Now, as to the total effect as to percentage, prevalence, however you define that, embryo toxicity I gather is 100 percent if the window is appropriate when the drug is given. The neuropathy ranges, in my estimation looking over the clinical information, from 60 percent. It may be higher than 50 percent. So, that needs to be better clarified as stated.

Some of the hematopoietic changes, specifically the low white counts, perhaps need to be dialed up a little bit to more carefully.

But on a whole, we do know the safety parameters and where the issue areas are, and so again, I'd answer that question yes.

DR. McGUIRE: Well, that just goes to show you.

You and I have the same information, Wilma, and I would vote no on it because I think the axonopathy has not been adequately described and we don't have predictive measurements.

DR. CRAWFORD: Could I just add or just repeat that the British experience is the committee has recommended sensory action nerve potentials to be done on all patients before they start thalidomide.

DR. McGUIRE: I can't hear you.

DR. CRAWFORD: The Committee on the Safety of Medicines in the U.K., the equivalent committee to this one, has recommended that sensory action nerve potentials be done before any patient is given thalidomide.

DR. McGUIRE: Okay.

DR. MATHEWS: Dr. McGuire, could I make one follow-up comment on that?

DR. McGUIRE: Please do.

DR. MATHEWS: Perhaps because of my experience on the Antiviral Committee, at least in HIV-related applications, we have used for over 10 years medications which have predictable neurotoxicity and because of the severity of the underlying disease, those risks are taken. In some cases, it's clearly dose-related; other cases, not so.

So, in my mind, it depends on what is the

indication for the treatment, what are the other treatment options. Of course, it's not only in HIV medicine. In oncology routinely these drugs with neurotoxic potential are used. So, it's not in my mind a question, does it cause it or doesn't it? Is it severe enough? Is it reversible and is it worth the risk?

DR. McGUIRE: The question really is whether we've described it fully, whether we know what we're dealing with. It's not whether it's a neurotoxin or not a neurotoxin and whether the axonopathy is permanent. I think the question, as I read it, is whether it has been adequately described.

DR. BERGFELD: Or identified?

MS. COHEN: I would use the word -- it has been described and substantiated. I mean, you can have all kinds of things about safety, but unless it's substantiated, you really don't know if it's safe. This is all in the mind, but it's the actuality that it's about. It seems to me if it has been substantiated, that's the part of the safety --

DR. BERGFELD: I don't think any committee member here would say that the two major issues here are not the two that we've been talking about, the embryo toxicity and the neuropathy. I think that those are real and I think we all agree to that.

MS. COHEN: Yes, I understand that.

DR. McGUIRE: Dr. Miller?

DR. MILLER: Just one other area that was mentioned by the reviewers was the area of postural hypotension was I think 12 percent in healthy volunteers, but there were no data for the patients with leprosy.

The other question gets back to the teratogenicity issue, what are the long-term effects on reproductive potential.

DR. KILPATRICK: Joe?

DR. McGUIRE: Yes.

DR. KILPATRICK: I think it depends how you read and interpret the question. From my point of view, I would vote no. It has not been adequately described because we don't have point estimates and confidence limits. There have been all sorts of figures thrown at us. I'm not denying the knowledge of the existence of these effects, but in terms of precise knowledge, I don't think we have it.

DR. McGUIRE: Yes. That's amazing. I think you and I agree 100 percent.

(Laughter.)

DR. McGUIRE: Yes.

DR. ORKIN: I'd like to ask Dr. Miller to clarify. I think I made an implication of the point that

you made yesterday and I wonder if we're on the same wavelength. Are you talking about pregnancies in the future, not toward the end of the current pregnancy, but what happens 10 years --

DR. MILLER: Right.

DR. ORKIN: Then I would agree with that completely.

DR. MILLER: It got to the issue of what happens to this drug and what does it do to sperm. Wilma brought this up several times yesterday too. Is it deposited in fat or wherever? And we just didn't know the pharmacokinetics of the medication.

DR. McGUIRE: Mr. Warren.

MR. WARREN: I know I'm just a layperson, but I have healthy brothers and sisters. Most of the thalidomiders who are the oldest child quite often -- their parents went on to have other children just for posterity's sake I guess.

DR. McGUIRE: I think most of us would be happy for you and your family, and we'd like to see a larger data set.

(Laughter.)

DR. McGUIRE: I think we've beat up on this question pretty much. I'm ready to vote. Fred, do you mind going first again?

DR. MILLER: No.

DR. McGUIRE: We are doing question number 2. Has the safety of thalidomide in the treatment of systemic ENL or any subset of ENL, such as cutaneous ENL, been adequately described?

And Dr. Miller says no.

DR. HASHIMOTO: Well, yesterday someone mentioned that TNF-alpha increases or fluctuates -- not very certain. But in the literature, TNF-alpha induced HIV -- activated or enhanced expression of HIV. If the drug goes to AIDS patient community, this issue wasn't addressed.

The other one is erythema nodosum is often a complication of birth control pills. Actually that's one of the most common complications of young female patients. If a patient is put on birth control, what happens if a large population trial goes on? Maybe erythema nodosum may be added on ENL. That issue we haven't discussed yet.

So, I'm not quite sure all the possible risks are disclosed at this point. So, I should say no.

DR. McGUIRE: Thank you.

Mrs. Cohen.

MS. COHEN: No.

DR. McGUIRE: Jim, you haven't changed your vote just because I voted with you.

DR. KILPATRICK: No. That is, no, I haven't changed my vote. On number 2, as amended, I vote no.

DR. McGUIRE: Dr. Simmons-O'Brien.

DR. SIMMONS-O'BRIEN: No.

DR. McGUIRE: Okay, McGuire, no.

Dr. Bergfeld.

DR. BERGFELD: I'm voting yes.

DR. McGUIRE: Dr. Orkin.

DR. ORKIN: No.

DR. McGUIRE: Dr. Mindel?

DR. MINDEL: Yes. I don't like voting opposite everybody all the time.

(Laughter.)

DR. MINDEL: It seems to me in the first question "demonstrated" is a very strong word. I find "defined" is a much softer word. Dr. Kilpatrick talked about confidence limits in terms of defined. I'm a little perplexed by that.

DR. McGUIRE: Well, Joel, I think it's okay for you to vote yes.

(Laughter.)

DR. MINDEL: But I find that the question is a lot softer, and I can vote yes for it.

DR. McGUIRE: Okay.

Dr. Mathews.

DR. MATHEWS: I vote yes also and it primarily relates to the experience of the physicians who have taken care of these patients. While I don't doubt that there is some clinical neuropathy in perhaps a significant proportion, if it hasn't observed and diagnosed, then I suspect it's not as clinically significant.

DR. McGUIRE: We have a vote for Dr. Duvic?

DR. BERGFELD: I'm sorry. Yes, we do. Yes. She votes yes.

DR. McGUIRE: She votes yes.

And Dr. Crawford?

DR. CRAWFORD: I vote no.

DR. McGUIRE: Oh, he's not voting.

DR. KILPATRICK: Dr. McGuire?

DR. McGUIRE: Yes.

DR. KILPATRICK: May I point out that Dr. Duvic who voted yesterday was probably answering in terms of the original questions and not the amended questions and that may make a difference.

DR. McGUIRE: I'm sure that's right. Just note that, Tracy.

We're moving right along to lunch. What I would like to do is to get started at 1:10 here and we'll begin with discussion of question 3.

(Whereupon, at 12:14 p.m., the committee was

recessed, to reconvene at 1:10 p.m., this same day.)

AFTERNOON SESSION

(1:16 p.m.)

DR. McGUIRE: Good afternoon. This is the last session of meeting number 47, and we are now into the part of the meeting in which the agency has asked us to consider a number of questions. Today we have eight questions. We've covered two of them, and I hope those were the hard questions, but we'll see.

(Laughter.)

DR. McGUIRE: We don't need to introduce anyone. I think it's the same cast that we had this morning.

Let me read question 3. Do the benefits outweigh the risks of Celgene's thalidomide in the treatment of systemic ENL syndrome or any subset of ENL, such as cutaneous ENL; i.e., does the committee recommend that Celgene's thalidomide be approved for systemic ENL syndrome or any subset of ENL, such as cutaneous ENL?

Once again, that question needs reading several times, and it gets a little more complicated on each reading. So, I think I'm going to strip it to do the benefits outweigh the risks, and then we can talk about cutaneous ENL versus other systemic forms of ENL.

Janet, how say you? Do you want Celgene left in here or out of here?

DR. LUMPKIN: No, out.

DR. McGUIRE: Out. Okay. Did everyone get that? We're talking about thalidomide global.

Actually, Tom Rea, where are you? Dr. Rea, who has been mentioned in the meetings many times, is a very experienced clinician and leprologist. Tom, if you could give us just a couple of minutes on thalidomide risks and benefits.

DR. REA: Yes. I have been using thalidomide since 1971 and approximately experienced with about 300 patients with at least four different forms of four different drug products being administered and getting a good response with all four.

The risks and benefits. I think the benefits are large.

The population of patients are those pretty much at the bottom of the economic barrel. A lot are illegal immigrants. A lot are recent immigrants to this country trying to hack it, and as most of you know, that is not necessarily easy. Then they're not particularly happy with the diagnosis of leprosy, but they can function with that diagnosis and they can accept that diagnosis and they can work or raise their family with that diagnosis.

When the acute ENL comes on -- and it's episodic and these episodes can be infrequent or they can

be occurring unremittently every three or four days.

The real therapeutic choices are high dose of steroids, and we certainly have patients where we've chased up to prolonged doses of prednisone at the level of 60 milligrams a day, which inflicts its own cost and does not give particularly good control.

When these people are started on thalidomide, whether they've been on steroids before or not, the response is usually quite striking, within a week. For the patients it means that they can go back to work and when you're at the bottom of the barrel economically, this is very important because the employers with these people are quite ruthless usually and if they don't show up for work, they're soon out of a job.

So, the benefits here are enormous when you consider that most of these men are fairly young, they have young families. The median age of our patients I think at the onset of ENL is in their mid-30s, so they usually have families and plenty of mouths to feed.

The difficulties that we encounter with the medication are usually overcome quite easily. The somnolence. There is a tachyphylaxis to that or the dose can be reduced or steroids can be added in a fairly low dose, say, prednisone 20 milligrams a day, and get a very good result.

For the men, it means that they can function and they can work and they can support their family. For the women, it means that they can take care of their children rather than lie around the house in bed much of the time and really neglecting their family because they are simply not well enough to do what they do.

I would accept actually greater risks than what the present proposal allows. For example, I would welcome returning to the time from 1971 to 1975 when we could use thalidomide in women who were on two methods of birth control. We did that. We selected patients very carefully. They were reliable. They kept their clinic appointments and they understood what was going on.

The neuropathy. I concede there is a -- and the patients know it. They have informed consent. We have not really seen what we would call a clinical progression in the peripheral neuropathy which virtually all have at the beginning.

This has been for these people a marvelous boon. For the County of Los Angeles, the amount of money that they have saved by keeping these people out of the hospital must be a considerable amount of money because prior to use of thalidomide, a lot of these people were in the hospital for prolonged periods of time.

There is no question in my mind that the

benefits that I have seen well outweigh the risks.

I expect that over time in any kind of protocol, eventually that a thalidomide baby will be born and it will be a very sad day, and I don't know what I will do when I look that child in the eye or that parent in the eye.

I am here as an advocate for the patients that I am taking care of, and if I cannot be their advocate, I really don't know who will be.

Thank you very much, Joe.

DR. McGUIRE: Tom, wait just a minute. Would you weigh in on cutaneous ENL versus systemic ENL?

DR. REA: The way we practice in our clinic and we see starting in two ways. One, it can arise full-blown like Venus in the half shell arising virtually overnight, the full-blown systemic syndrome.

It can also start occurring as the small dermal nodules looking a lot like mosquito bites occurring in various numbers, arising in crops, occurring intermittently. We usually note that down as incipient ENL, but don't treat it because the patients aren't sick yet. We don't want any more thalidomide out there than absolutely necessary. When the systemic symptoms develop or when the cutaneous lesions become interfering with one's occupation, then we treat. Usually they are systemic.

In the L.A. data that you read about, the 52 percent that were free of skin lesions, there was a remainder called a partial response by Dr. Weintraub's interpretation. By our interpretation, if they were free of the systemic part of the disease and just a few skin lesions, we considered that a good response. Actually, we like to see those few almost asymptomatic lesions because it lets us know that the patients really need to continue this medication.

So, our treatment endpoint is the control of the systemic aspects of the illness with a little bit of cutaneous lesions being very acceptable because when such people do fail to keep a clinic appointment and run out of their thalidomide, they exacerbate very quickly.

DR. McGUIRE: How much do you dispense to a patient in terms of days, weeks, months?

DR. REA: We usually go up to 200 milligrams, and if there is not what we consider a complete systemic response, we add prednisone. The reason why is I do not want people on 300 milligrams a day driving on the freeways to come into the clinic. That seems to be a very bad risk to take.

The length of time. Initially we will see the patient back in a week and then adjust the dose.

DR. McGUIRE: That's an entry patient.

DR. REA: That's an entry patient.

Once stable, we are now using 3 months as our routine.

We have a young man from the Philippines whose job is with a fishing fleet off of Alaska, and he can only come to the clinic twice a year. We are keeping him on the job, Joe, and maybe bending the protocol a little bit.

DR. McGUIRE: Let me ask you a rather loose question. What do you think the incidence of noncompliance is if we consider noncompliance to be using the medicine for some other issue or giving the medicine to someone else or not returning to clinic at the expected date?

DR. REA: The returning to clinic at the expected date I think is much higher with the patients on thalidomide than it is on the routine because they know that this medication is keeping them out of trouble. Where for, say, an ordinary lepromatous patient who doesn't have any reactional state, that is, they're not feeling terribly ill anyway, so there is not as big a premium in returning as there would be if you were on thalidomide.

I don't know how much goes on of that. We've got no way to really check on it. We can tell when the patients say they don't need any more thalidomide and if they were taking one a day, they should have run out. We try with a fair degree of accuracy to have the patients

routinely bring in all of the medications that they are on, so we will try and get some handle on what's going on.

They are cautioned at the beginning and we do try to reiterate repeatedly that this is a drug that nobody else in the family should take, and in a pregnant woman, it is devastating.

DR. McGUIRE: Tom, if you would just stay there, maybe other people from the advisory committee could question you. Dr. Orkin has a question.

DR. ORKIN: Have you seen, Tom -- and I think you may have already intimated -- any pregnancies?

DR. REA: No. We have not seen any pregnancies in women on thalidomide. We have seen, going back over 20 years, at least one of the women on thalidomide, which was discontinued subsequently, she had had no children at that time. She was about 18 years old and now has I think two or three children. I don't know just when they were born. I think the first one was probably about a year after the thalidomide was stopped.

DR. ORKIN: Also, have you seen them on their own use it for other conditions or pass it on to somebody else?

DR. REA: We have not knowingly observed it. Whether it has happened or not, I really don't know. The nightmare that has not yet become a reality is the, quote,

sterilization with tubal ligation, which has a failure rate of around 1 percent.

DR. McGUIRE: Are there other questions from the committee? Dr. Hashimoto?

DR. HASHIMOTO: Do you see any great need for making this prescription drug released out of the institution? What is the reason, if any, that this should be outside of the institution?

DR. REA: As an advocate for my patients, I think it is important that there be a good supplier, a reliable supplier within the United States. Otherwise, they are at risk. We had, as Dr. Yoder mentioned, a crisis when Chemie Gruenenthal took the stuff away and there was a short supply. I don't think there's any real hardship there.

But as an advocate for my patients -- and I'm under this privileged umbrella. So, that is why I am here. But as a physician who has seen a group of patients benefit greatly, I expect there are other patients that will benefit greatly with other diseases, as witnessed, the Behcet's syndrome.

DR. McGUIRE: Dr. Rea, which suppliers are you using? Are you using only the Celgene product?

DR. REA: No. I have never used the Celgene product. We started out with Chemie Gruenenthal, then the

Carville kind of Tulane homegrown supply, then the Brazilian tablet that was sort of like chewing on marbles. I don't know if any patients broke their teeth on it. They might have. And then the Brazilian product that comes as a capsule.

DR. McGUIRE: Dr. Miller.

DR. MILLER: Just two questions, Dr. Rea. The first one is, do you worry about the sperm with these gentlemen?

DR. REA: This was actually looked at in the 1960s, and there was no evidence. If you're taking lepromatous men, that is a very poor place to start to look because untreated, lepromatous patients, or treated -- there was no difference in our data -- 85 percent have an elevated FSH. 80 percent have an elevated LH. About 33 percent have clearly subnormal testosterone levels, and male infertility is not an uncommon complaint. It is not easy for a machismo Mexican male to admit to this or a retarded libido, so I expect the complaint is much more prevalent just judging by our own biochemical data.

DR. McGUIRE: Mrs. Cohen?

MS. COHEN: Go ahead.

DR. MILLER: I have one more question. How do you select which subset actually receives thalidomide? Is it all patients with ENL or how many lesions do you need

and how do you define that?

DR. REA: It's the being ill with it. There is no magic threshold on a numerical count. It's not like neurofibromatosis. You got it if you got six or seven cafe au lait spots. That is not the therapeutic motive. The therapeutic motive is you have a sick patient. It's like perhaps analogous to when a patient goes to garden variety psoriasis to pustular psoriasis, von zumbush, you got a sick patient on your hand and you're going to wheel out a big gun. And steroids won't do much good either.

DR. McGUIRE: Mrs. Cohen.

MS. COHEN: How many patients do you have, men and women, and how many are successfully treated and leave?

DR. REA: As of the end of 1996, under the Carville IND, we've had on thalidomide 291 patients. If I include those that have enrolled this year and those that enrolled in the early 1970s, it is certainly over 300. I think at the end of 1996, the last time I counted noses, we had close to 50 patients receiving thalidomide.

MS. COHEN: Is that a pretty steady amount?

DR. REA: It has been higher in years past. When the Vietnamese immigration to this country was at its peak in the mid-1980s, we were at a higher level. We were up to about 60 or 65.

DR. McGUIRE: Susan, let me ask another part of

your question. How many patients are you accessing per year now? Let's say for 1996 or 1955. I'm not talking about patients in the system.

DR. REA: How many new ones?

DR. McGUIRE: Yes.

DR. REA: This year there have been approximately 10 patients so far. If you want to reduce the number of leprosy patients in your clinic, a good way to get leprosy control is to get politicians to start to blame immigrants for all of your local problems. These people are very sensitive to what's going on, and there was a big drop in our numbers of cases when proposition 187 was passed. And that trough lasted for about a year, and I think we're getting a little wave in response to that trough now.

MS. COHEN: I'm still curious to know in terms of treatment how long you keep them and are you successful? How often do they leave? And also, if they're really illegal aliens, I'm surprised that they would come in a system and even identify who they are.

DR. REA: The one question we never ask is their immigration status because that is an inherently pejorative question and an intimidating question.

Dr. Yoder's figure of the mean time on thalidomide was 3.3 years. I expect ours is a little

longer. We've got a lot of Mexican men and they seem to be a prime candidate for prolonged -- we have a few patients that are pushing the 10-year mark. Just flying by the seat of my pants, I expect the median time is about 5 years.

DR. McGUIRE: Yes.

MR. WARREN: I was just wondering. You said some people took themselves off of thalidomide.

DR. McGUIRE: I recognized Colin. Just a minute. Go ahead.

DR. CRAWFORD: Presumably these patients are on multi-drug therapy, including clofazimine. Do you think the frequency and the severity of ENL has diminished?

DR. REA: I can't answer that question. We don't use a lot of clofazimine. Dr. Gelber and I did a study 10 years ago where 1 out of 101 patients were dapsone resistant. The rationale of including clofazimine is to cover bets that patients might have a primary dapsone resistance. That's the rationale for triple drugs.

The people in Brazil say since MDT has come along, there is more ENL and more reversal reactions than what there was before. I cannot comment on that.

DR. McGUIRE: Mr. Warren?

MR. WARREN: I was just wondering. You said some people said they took themselves off of thalidomide. Do they bring back the pills?

DR. REA: That is not a very dependable thing. We do ask them to flush them down the toilet. We are not worried about malformed rates in the sewer system. But there's a strong injunction for them to get rid of it. It's an excellent suggestion to ask them to bring it back. I don't know what the compliance rate would be on that, but it's a very good idea. Thank you.

DR. McGUIRE: Tom, your testimony is very helpful. Are there other questions from the committee?

(No response.)

DR. McGUIRE: Thanks very much, Tom.

DR. REA: Thank you, Joe.

DR. McGUIRE: What other questions do we have about the risk-benefit ratio? Dr. Lumpkin, you're getting closer and closer to the microphone.

(Laughter.)

DR. LUMPKIN: That's why I raised my hand.

The only thing I would like to say in relation to this question, when we were forming the question, clearly as the implication is, this is the question where we're asking do you think this should be approved for this indication or not.

I think what's always hard in trying to put these questions together is for the committee to say -- we're asking you to look at the entirety of the system in

which it might be used here. Do the benefits outweigh the risks?

Now, obviously if we were saying do the benefits outweigh the risks for the use of this product over the counter, that would obviously put people in one frame of mind. And that we are not.

Obviously, as has been said here previously, we're talking about use if this product were to be approved as a prescription product.

But as we get into some of the other questions, I would just say, as we say to all of our committee members, think about it and if there are caveats that you think are important in trying to come to your benefit-risk equation here, this is the time to put those forward. I just didn't want people to be confused. If you think the benefits outweigh the risks if this thing were labeled in a certain way or if you think this thing were in a restricted distribution pattern or if you did neuropathy screens or whatever, if there are caveats, by all means put them in. We don't mean for you to take it in kind of a blinded fashion or a blinder fashion.

DR. McGUIRE: Thanks very much, Mack.

What we're doing is anticipating questions 5 and 6 and some of the other issues that will be dealt with. So, rather than deal with all of these issues at this

moment, I would rather deal with the safety/efficacy, and then we will observe question 4, what additional information, and then go right ahead to questions 5 and 6.

Is there more discussion before we move? Yes.

DR. MOORE: I'd just like to make a brief comment. I believe this is an extremely difficult task for the committee because we're talking about risk to the patients themselves and risk to our next generation. But I would respectfully ask that the committee realistically consider the risk as being not only for use in ENL but also for many other conditions, some of which will be more prevalent in women of childbearing potential.

As I mentioned yesterday, we had had some discussions with a couple of individuals who work at Carville who now say they only have 5 patients who are on this drug for ENL and have enough thalidomide stockpiled for the next millennium. So, we're really talking about the risk for a much larger group of patients.

DR. McGUIRE: That's an important observation. It has come up several times in the deliberations and it will come up again after we take care of the risk-benefit issue.

So, I'm ready to ask how you feel about the risk-benefit. Cynthia, we can start with you.

DR. MOORE: I'm not on the committee.

DR. McGUIRE: Oh, you're not voting. Well, all the more reason.

(Laughter.)

DR. McGUIRE: Chris. Dr. Mathews.

DR. MATHEWS: Understanding the question as you formulated it regarding ENL patients, yes, I think it's clearly a favorable risk-benefit ratio.

DR. McGUIRE: Dr. Mindel.

DR. MINDEL: Yes, I think it's clearly favorable.

DR. McGUIRE: Dr. Orkin.

DR. ORKIN: Yes.

DR. McGUIRE: Dr. Bergfeld.

DR. BERGFELD: Yes.

DR. McGUIRE: Dr. McGuire, yes.

Dr. Simmons.

DR. SIMMONS-O'BRIEN: Yes.

DR. KILPATRICK: This is Kilpatrick speaking.

DR. McGUIRE: Dr. Kilpatrick.

DR. KILPATRICK: I should point out that the ultimate authority in my life, my wife, has just walked into the room.

(Laughter.)

DR. KILPATRICK: So, I have to be very careful in what I say, but she knows me well enough to know that I

am somewhat perverse and I vote no because, again, as I read the question as changed, I tend to look at things not from a patient perspective, from a population perspective, and I am not convinced that the benefits outweigh the risks in a population sense. In a sense, I have no information on this because no information has been collected that would convince me otherwise.

DR. McGUIRE: I think the question is framed so that we're talking about the population with ENL. We're not talking about general population problems, which is another issue that we have to deal with in a few minutes.

DR. KILPATRICK: In that case, not being a clinician, I defer to my colleagues.

DR. McGUIRE: Which one?

(Laughter.)

DR. KILPATRICK: Anyone but yourself, sir.

(Laughter.)

DR. McGUIRE: That proves that I'm a neutral chairman. That's very important.

Mrs. Cohen?

MS. COHEN: If it's just the ENL, it still is a distribution problem, and I need to know what plans there are for distribution. I mean, it isn't just the risk. This is a very complicated question that really involves a lot of things. It isn't just giving it. It's how do they

get it, how do they monitor it, and what additional information, which is the next question. I must have about 20 things written here as to what information I need more before I make that decision. So, I have to in good conscience say no.

DR. McGUIRE: Okay.

Dr. Hashimoto.

DR. HASHIMOTO: I shall say yes, as far as this definition of ENL limited efficacy is.

DR. McGUIRE: Dr. Miller.

DR. MILLER: Yes. Again, with the subset clearly defined as Dr. Rea pointed out.

DR. McGUIRE: Thank you very much.

Question 4 I'm going to read because I think question 4 is really a segue.

DR. BERGFELD: Excuse me. Did I say that Dr. Duvic said yes?

DR. McGUIRE: Yes, and her vote would count if that question has not been changed, has not been altered. And the question has been altered so that "Celgene" now reads "all thalidomide." So, someone else can consider that, but as I understand it, her vote would not be counted.

Does anyone want to tell me better?

A little side bar there that I didn't understand.

Question number 4 is what additional information, if any, should the sponsor be asked to provide before approval can be considered?

Now, this is a very big question and I'm not going to deal with it head on. What I'd like to do is go to question 5 which will carve a little piece out of question 4. If that's acceptable to the advisory committee, could we go directly to question 5? No objection? Thank you.

Question 5 is, can Celgene's thalidomide be safely used only if distribution or use is restricted? If so, what kind of restriction of distribution would the committee recommend?

Dr. Lumpkin, I gather here we would also eliminate Celgene?

DR. LUMPKIN: Yes, yes.

DR. McGUIRE: So, can thalidomide be safely used only if distribution or use is restricted?

I don't think we even have to vote on that. Let me say yes and see if anyone disagrees. Does anyone disagree that it should not be restricted?

MS. COHEN: I hate to tell you that I reworded the question.

DR. McGUIRE: Susan, you would like to what?

MS. COHEN: I reworded the question.

DR. McGUIRE: Go ahead.

MS. COHEN: Should thalidomide be safely used only if all the criteria of the FDA be met and any distribution be highly restricted under a fail-safe plan?

DR. McGUIRE: Okay. We can deal with all of those restrictions in a moment. If we will just answer the first part of that. Can thalidomide be safely used only if distribution or use is restricted?

My sense is that the committee feels that it should be restricted.

DR. BERGFELD: I think adding to that would be mandated and monitored.

DR. McGUIRE: Okay. Well, then let's talk about what kind of restriction of distribution, what kind of monitoring would the committee recommend.

DR. KILPATRICK: Mr. Chairman?

DR. McGUIRE: Yes.

DR. KILPATRICK: I'm in the position where I'm uncertain that any type of restriction or limitation of distribution can effectively meet the criteria which I would like to see. So, I'm maybe not answering the question, or am I again off in left field?

DR. McGUIRE: No, you're not off in left field. But I think we should take a serious attempt at defining what restrictions there should be that would give us some

degree of comfort.

Can we protect every consumer from this drug? If you're asking that question, I think everyone, beginning with Dr. Hanson yesterday who spoke for the American Academy of Pediatrics, thinks that once the drug is out there, there will be misuse.

The question is, is it possible to control its use and what regulations do we build into its use?

But the question you're answering, if you want an absolute answer, I think it is not possible to provide absolute assurance, and I accept that as a fact.

But the question is what should we be doing. Should we simply give up at this point and say we could not provide enough safety --

DR. KILPATRICK: I see. I understand.

DR. McGUIRE: So, let's have some discussion. Dr. Bergfeld.

DR. BERGFELD: I'd like to add to my comments of mandated and monitored restricted distribution that this be specific for ENL and that any other uses be subject to INDs and future NDAs.

DR. McGUIRE: That's a very important issue. I hope everyone on the committee understands it. We are talking about restricting the use of thalidomide only for the treatment ENL, not the other disorders for which it

might be used, and I support Dr. Bergfeld's suggestion.

Chris.

DR. MATHEWS: While I'm in great sympathy with what the goal that you articulated is, I think we should consider what are the problems with the current distribution system under the IND mechanism. I'm sharing with you very small experience but enough to make me concerned that the present system is not adequate in the controls in place.

My experience with this drug was in participating in a clinical trial in HIV wasting. I think we enrolled 7 patients. There were no problems that came to my attention as the local investigator on that study.

The IND mechanism. I've treated 2 patients within the last year and a half, had to get IRB approval, had to get the FDA to give me an IND number, had to call through a list of companies that they gave me the names of that were willing to make the drug available. That takes a lot of time, so I was in sympathy with that family practitioner whose letter was read yesterday on how difficult this can be.

Having said that, I have one patient who came into my practice having obtained thalidomide for aphthous ulcers from another physician a year previously. He still had a supply of the drug, and a couple of weeks ago had an

outbreak of severe aphthous ulceration. I phoned in a prescription for prednisone because I knew I couldn't get thalidomide right away. He says, oh, I have a bottle right here. How about if I take that? So, there are people out there with this drug.

The other case was even more disturbing. This was a young man who was deaf and dumb who had horrible aphthous ulcerations and he had lost 40 pounds because he couldn't eat. He finally agreed to take thalidomide. We got through the approved mechanisms. He took it. The ulcerations healed completely. He gained weight.

And one day he showed up in the clinic and told our pharmacist that he wanted another bottle of thalidomide, which we didn't have, and his ulcers were healed, so we didn't pursue it.

Shortly thereafter, it comes to my attention that one of the practitioners in my clinic, which is an academic clinic with about 20 different people working there, had another patient with aphthous ulcers, a woman who came in with horrible disease. It just so happens that the patient, the gentleman who was deaf and dumb, had brought in this huge bag of medicines, one of which was a bottle of thalidomide, properly labeled. And she, who wasn't involved with obtaining the IND or anything else, took some pills out of that bottle, put it in a sterile

container cup, and gave it to this woman to take for her aphthous ulcers. She fortunately knew enough to make sure she wasn't pregnant and all this.

Well, you can imagine. I went ballistic, contacted the IRB and everything else. But this is in a fairly sophisticated medical care environment.

As I saw the presentation yesterday of the educational program that was planned, if this drug is ever licensed, the use of blister packs, label things and so on, a lot of these little incidents, many of which nobody knows about, would be more likely to be prevented.

So, I don't think the simple IND mechanism, by way of sharing these anecdotes, is a fail-safe system and needs to be improved.

DR. McGUIRE: Well, I'm glad you shared those clinical experiences. That must have been a terrible week.

(Laughter.)

DR. McGUIRE: I can't imagine what I would tell my IRB if that happened to me. Well, I would tell them the truth, but I don't know what would happen to me.

Is there more discussion to the point? I think the question is can we make the existing system better or is the existing system going to continue as it is at least with regard to ENL. Dr. Bergfeld's point I want to leave out there because, as far as I'm concerned, we're talking

about ENL at this point, and the recommendations that we will give the agency for controlling the drug and providing the drug, we're restricting that to ENL.

Is everyone comfortable with that? Yes? Susan, you're saying no. You want to restrict it to another disorder, or you want to open it up to other disorders?

MS. COHEN: I'm not being contentious. I just am concerned about the distribution, and if Chris is an example, it's probably a small example of what happens. There are so many things that are unanswerable and ponderable in all of this. It's like you have already decided that the distribution is going to be fail-safe, it will be wonderful. I really don't know. I've seen their package. I've seen what's here.

When I asked yesterday about the experience we've had in this country with the buying clubs and what's happened, that was not a facetious question. That was a question to know what the actuality is and what's really going on out there. I have been told that there's thalidomide out there on the streets.

DR. McGUIRE: There is.

MS. COHEN: So, I don't know how to answer because I don't understand enough. So, I have to pass because I need to know more, and if I don't know more, it

isn't fair for me to vote on what I don't think I know. But that's just me, and remember I come from a consumer protection background.

DR. McGUIRE: Thalidomide is out there, and we're talking about a specific application of thalidomide for a disease and can we control it.

Susan, you know, I don't believe there is a fail-safe system for anything I can think of.

MS. COHEN: But at least we can try. That should be our standard.

DR. McGUIRE: And so, what we're attempting to do is to craft a program that will protect as many people as we can and provide benefit.

MS. COHEN: I understand. Chris mentioned IND. I'm intellectually curious. I want to know how you're going to do it, how you're going to restrict it. I understand the fever in the ENL. That much I understand, but I don't know enough about the distribution.

DR. McGUIRE: The granting of an IND controls the process only at a single point.

MS. COHEN: I understand that.

DR. McGUIRE: And this is a multi-point process.

MS. COHEN: And that's my concern.

DR. McGUIRE: And this is what we're attempting

to address now.

Dr. Hashimoto.

DR. HASHIMOTO: Well, considering only a very small number of ENL patients treated right now, and considering that current IND program working fairly well, unless someone really push for off-label use, I really don't think any need for releasing this medicine for prescription category. If you talk about ENL, that's a very small number of patients. The company probably never makes money on that. So, there are different interests in this procedure. But current program, as I hear from experts, it's mostly institutional and working very well. Why not change at this point?

DR. McGUIRE: Ken, that's an excellent point and I hope everyone understood Dr. Hashimoto's issue.

The financial issues, whether they bring the drug to market, are not of concern to me. That's their decision, and they can decide the market is too small, too large. That's their decision.

You have heard from Dr. Mathews that the IND doesn't protect the public. As I mentioned earlier, that is a control only on one point in the process. So, we're looking at ways to protect the greatest number of people.

And the issue as to whether the market is large enough to support their effort, I think that's not -- well,

I'm not going to worry about it.

DR. KILPATRICK: Dr. McGuire?

DR. McGUIRE: Dr. Miller. Oh, I'm sorry. Dr. Kilpatrick.

DR. KILPATRICK: I just want to make sure that I understand, not being a clinician, what is being said. Dr. Hashimoto, do I understand that under the current IND rubric, only caregivers are dispensing the drug to patients or are patients being given drugs to take home and self-medicate? If the former, I would think that would be much more secure than sending supplies home with individuals.

DR. HASHIMOTO: Well, actually IND is a program which individual institutional physicians should apply to FDA and justify the use and documentation and then drug distribution. Drug is given to patient. Patient can take a drug home or whatever, but it's under control, supervision.

DR. McGUIRE: Dr. Rea addressed that, Jim. His patients take the drug home for 2 weeks, 2 months, one patient 6 months. So, the drug is dispensed under that program to the patient.

Dr. Miller, you had a comment?

DR. MILLER: No.

DR. BERGFELD: Can I enter here?

DR. McGUIRE: Dr. Bergfeld.

DR. BERGFELD: The package that we saw in the communication package, which was the educational package, dealt with a number of individuals being put into the safe program or they hope to make a fail-safe program. And that included the pharmacists, which was an interesting idea, where it would be a monthly prescription only, not a bag of pills for six months, and the individual with the prescription would have to present with it certain documentation to have the refill, not just the prescription. That certainly is better than what we have right now. Just that one piece is better than what we have right now.

DR. McGUIRE: Absolutely.

Dr. Mathews.

DR. MATHEWS: My evolving thought on this is that what needs to happen is that whenever thalidomide is dispensed for whatever reason, whether it's under an IND or part of a prescription program, that there be a uniform educational package which I should think the agency would review and sign off on, rather than what's happening now where it's just sort of an ad hoc process with every institution having to sign off on something with no clear uniformity of what's required even at the local level.

DR. WOODCOCK: That's one of the subjects of the meeting next week. There are many new indications or

diseases under investigation for treatment with thalidomide. The goal is to have some uniformity of message. As Lou Morris said yesterday, the most important thing is to know what your message is and have a consistent message and program out there.

But with the situation that has been present in the country -- and I think Debbie Birnkrant knows most about this -- for quite a long time we've had no consistent sources of product, and therefore we haven't been able to ensure this kind of uniformity and sort of regularization of the product.

DR. McGUIRE: That's very important and added to the anecdote that you heard from Dr. Mathews, which is that the current method of distribution is a very leaky method. It's a very dangerous method. So, at the very least, we can improve what's happening.

Milt, do you have anything to say?

DR. ORKIN: I was just thinking and this is probably redundant and already been addressed, but perhaps I can address this to Dr. Woodcock or anyone else.

When they order the prescription for the thalidomide, clearly a date is put on and perhaps no refill, and would it be appropriate, must be transmitted to the pharmacist by a certain date? In other words, put a restriction on it to avoid the refills that may be

that's certainly something we could do and we'd like to hear more discussion on that.

DR. ORKIN: There's also the implication that it be filled by the same pharmacy so that pharmacists would have some input in terms of the continuity.

MR. WILLIAMS: Yes. The other thing is that the way the system is being developed, it would be designed to utilize some of the systems that are currently in place within pharmacy practice where there are central computer databases that pharmacists log in and out on when they are filling prescriptions. A portion of one of those databases will be carved out to actually have the pharmacist tracking and recording information on this patient so that we'd be in a position to monitor that the pharmacist was in fact complying with the program.

DR. McGUIRE: Yes, Cynthia, go ahead.

DR. MOORE: I have a question for you, a little bit of follow-up of what we talked about yesterday when I asked if somewhere on this documentation would be the patient's diagnosis or the indication for using it, and you said yes.

MR. WILLIAMS: Yes.

DR. MOORE: I guess my concern with all of this is that thalidomide may be prescribed for less than very serious disorders such as one or two aphthous ulcers in a

patient who's a non-HIV patient or some sort of indiscriminate use, using a very dangerous and powerful drug for something that is not life-threatening or not even terribly serious although certainly annoying in that patient.

You had at one point talked about looking for -- I don't know if I should call it failures, but times in which all of the measures that you had recommended weren't being followed and getting back to the pharmacy or the physician with this information.

MR. WILLIAMS: That's correct.

DR. MOORE: Does that include looking at the reason this prescription was written and making some sort of attempt to say back to that prescriber, you're prescribing this very powerful drug in a way it was never intended to be used and for a disorder in which there really is no data about its effectiveness?

MR. WILLIAMS: Yes. I guess it's hard to be specific in answering that question certainly because there's a lot of hypothesis in it, but I share the concern. The last thing in the world we would want is to see the drug used in what I will call somewhat judgmentally trivial indications or indications that are not serious. That to us would be unacceptable.

We have had some discussions with Allen

Mitchell and his colleagues in Boston because that data would first be coming in to them. I know in the current Accutane situation, if they see data coming in that suggests what might be inappropriate use, there is some follow-up if I'm not mistaken.

Allen, do you want to address that?

DR. McGUIRE: This is Allen Mitchell who has been tracking the Roche program for a while.

DR. MITCHELL: Yes. Allen Mitchell from Boston University, Slone Epidemiology Unit.

Just in the spirit of disclosure, we have been negotiating with Celgene, as Bruce had indicated, yesterday to perform a survey if the drug is approved.

In the Accutane survey, there was one component when we were doing a telephone arm of the follow-up where if we identified women who identified themselves as sexually active but not using contraception, we would read them what we called the riot act, which was a very stern warning about the risks of that kind of behavior and the need to discontinue drug immediately.

And I also asked them for permission if we could contact their physician since we maintain confidentiality and we couldn't contact their physician without their permission. And if we were given their permission, we would then contact the physician and inform

him or her of the practice as well.

That was for the patients who were identified through the telephone survey. That kind of mechanism exists in a survey mode. We haven't talked about it specifically in this context. It might be something worth pursuing.

MR. WILLIAMS: Yes. I think it's a very important consideration, Dr. Moore.

DR. McGUIRE: The issues that have been defined are the issues of a stale prescription would not be honored. A prescription would only be honored for a given length of time. A limited amount of drug would be dispensed, and the drug would be identified with the diagnosis. And then the post-marketing surveillance would be crafted by the company.

I think those are the large issues, but I'd like to hear if there are other things that I've missed. Chris?

DR. MATHEWS: There's a concern about the number of pharmacies involved with the program because the staff at pharmacies obviously rotates. It's possible to get an inexperienced person in who could dispense the medication without the proper fail-safe mechanisms in place and so on.

One option which could be considered is a very

restricted or even single distribution system as was done with one of the protease inhibitors initially in HIV medicine where they would be totally responsible for the quality control and have staff assigned who know that they're responsible and not dealing with hundreds of other medications simultaneously and in between.

DR. McGUIRE: Dr. Bergfeld.

DR. BERGFELD: One thing I think you left out in your list, Joe, was the fact that it might be very interesting and important to track the physician ordering and, when inappropriate, there be a means of contacting that physician.

DR. SIMMONS-O'BRIEN: Joe?

DR. McGUIRE: Yes.

DR. SIMMONS-O'BRIEN: I was thinking along the same lines as Dr. Bergfeld. We all hate long paper trails, but oftentimes they keep us doing the right thing. Maybe prior to the patient getting the prescription, whether the prescribing physician can send a letter to a designated pharmacist at the pharmacy saying that they would like for this patient to get this prescription and have that kept in some sort of file with the pharmacist saying that they are aware the patient is being treated for blanekty-blank and will be followed by this particular physician for ENL, but just have communication between those two people to go in

files on that particular patient.

My concern would be a physician who writes a prescription for a patient -- and hopefully they will have ENL -- and have no plans on following that patient and following them while they are on the medication.

DR. McGUIRE: Susan?

MS. COHEN: Since many Americans don't live near major medical centers, how do people who live in rural areas or small areas get treated, and how are they taken care of if they have these particular kinds of problems?

DR. McGUIRE: Who would like to address that?

DR. YODER: You're asking specifically about patients with ENL?

MS. COHEN: Yes, it can be ENL. Yes.

DR. YODER: I would be talking specifically about ENL.

This is a problem. It's inherent in the current system, and I would just comment on some of the problems with the current system.

Patients in rural areas -- and I know of a specific situation like that in south Texas where the physician does not have an IRB in the local hospital and therefore she has a problem getting this done. The patient consequently will either have to come to Carville or travel 75 miles or so to San Antonio where they have access to

thalidomide. So, it is a problem.

Another alternative is they can come to Carville, for example, and get thalidomide from there, but that is one of the limitations on the current system.

Certainly that's one of the things that could be relieved.

I think another comment I would make along the lines we were just discussing, certainly that accessibility would be an improvement, also the reporting that would be done under what has been proposed here would, in my opinion, be a definite improvement over what we have at the current time.

DR. McGUIRE: Thank you.

Dr. Bergfeld.

DR. BERGFELD: I just want to remind the panel that yesterday was presented a package of an educational package, along with the packaging and everything else. My remarks have been based on the fact that that is a done-did, that will be done. So, the education of the physician and perhaps signing off an informed consent and then having restricted use by a physician according to their training and whatever else is developed would be very important here.

DR. McGUIRE: Yes. I'm sorry. Dr. Miller.

DR. MILLER: Joe, could there be designated

pharmacies which would be contacted by the physicians who are prescribing and then the prescription would be sent to those pharmacies and then they in turn would send the medication to the physician who would dispense it to the patient? That would certainly keep it under some control, but you would have maybe six, seven centers in the country and then the physician specifically sends the prescription to that person with, on the prescription, what's being diagnosed.

DR. McGUIRE: Yes. That's a novel idea. Don't ask me if it can be done. I haven't any idea. The question is, where is there greater control? At the physician or at the pharmacy? I don't know. You need maybe both in place, yes.

Dr. Weintraub, this is not a yes/no question. You asked for restrictions, advice on distribution, ascertainment of diagnosis, lots of issues. We've talked about that for a while and you must have a lot of stuff on your yellow pad now.

DR. WEINTRAUB: It's white but I did take a lot of notes. As far as I'm concerned, you may move on.

DR. McGUIRE: Okay.

DR. MATHEWS: Dr. McGuire.

DR. McGUIRE: Dr. Mathews.

DR. MATHEWS: Let me criticize some of the

are other disorders for which it might be used. I think we should be wary of the off-label because that's where the biggest mistakes are going to be made and that's where most people are going to be at risk.

I think, as I mentioned yesterday, we need to make this system as leak-proof as possible. It's still, I grant you, not going to be a perfect system, but I think we should deal with the ENL issue and then the agency will probably pick up bits and pieces of our discussion and use them in other applications, including the orphan applications, and will attempt to eliminate, minimize off-label use.

Are you and I talking about the same thing?

DR. MATHEWS: Well, the point is that the drug is being used right now.

DR. McGUIRE: Oh, I understand that.

DR. MATHEWS: It's not off-label because there is no label, but it's being used for a variety of indications. In my judgment it should continue to be used under controlled circumstances. If ENL is the first indication for which a label is granted, then I'm hopeful that all of the mechanisms in place to ensure the quality of that distribution program are simultaneously applied to the other mechanisms of drug distribution.

In other words, I could envision something

unfortunate happening whereby a particular sponsor gets a label for one indication and has this elaborate system in place which works very well, but then every other physician who tries to obtain the drug will go through a list of six or seven suppliers, and all of the problems that are currently potential issues would be unchanged.

DR. McGUIRE: I think that is a regulatory problem. Janet?

DR. WOODCOCK: We hear you and we agree that this is a problem and we will do everything we can to try and deal with it, including the meeting next week which I urge people to attend.

DR. KILPATRICK: Dr. McGuire?

DR. McGUIRE: Yes.

DR. KILPATRICK: May I come back to a statement Dr. Moore from CDC made yesterday referring to off-label uses? She said, if I correctly quote her, that off-label uses should be banned or made illegal. Could you elaborate, ma'am, on that and tell us if that is feasible in any sense?

DR. MOORE: The last part of the question I think I would redirect back to our colleagues from FDA.

What I said was and what I gave yesterday were suggestions that individuals who attended our meeting in March of this year gave us, ways to limit fetal exposure,

and that was one of the suggestions that off-label use should be prohibited. It's not a recommendation from CDC. It's one of the suggestions.

But as far as whether that can actually be done or not, I can't really answer that question. I think that's a question for the other table.

DR. McGUIRE: Dr. Kilpatrick, did that meet your question?

DR. KILPATRICK: FDA has not responded, but I take it that their nonresponse means that it's not possible to affect off-label use. We're going in circles here. There is no label as yet.

DR. WOODCOCK: Right. It has not been done. This is not something that we have invoked. I think it would be very difficult. I think the question Dr. Mathews is raising is if we develop a perfect distribution system for ENL, are we sacrificing the practical and the best solution for the ideal?

We understand the sentiment and we will certainly take these issues under consideration. Thank you.

DR. McGUIRE: Would the committee please look at question 6 and see if there's anything to be -- we are not voting on 5. We have given the agency a lot and they don't need a yes/no. They're getting a consensus and a

strong feeling.

(Laughter.)

DR. McGUIRE: Let's go to issue 6 and see if there's anything left to be discussed there. If so, we should certainly do that at this time. Are there recommendations other than those associated with restricted distribution the committee would make regarding ways to minimize the risk and safety concerns regarding the product?

Well, we've talked about restricted distribution. We've talked about certifying physicians, certifying pharmacists, and putting a stale date on prescriptions, and several other issues.

Is there more to be brought to question 6? Joel?

DR. MINDEL: I was disturbed that there are buying clubs that can get the drug legally.

DR. WOODCOCK: No.

DR. MINDEL: No. So, this is illegal.

DR. WOODCOCK: Correct. We have taken legal action against the buyers' club and we have also talked to other buyers' clubs and ensured that they stopped making thalidomide available. But apparently it's still available. That's what the CDC representative said yesterday and other people have said it is still available

illegally. It's difficult to totally suppress this.

DR. MINDEL: I'm concerned a little bit that by being very strict in your control of the drug, we'll have the situation that we have now with cocaine where if I try as a physician to get some to test for Horner's syndrome, it's virtually impossible, but if I go down to the street corner, I can get all that I need. And we're going to have this situation with this drug.

DR. McGUIRE: Dr. Mindel, you bring up an issue that I would have given anything to have avoided today. Now that thalidomide has achieved the status of a street drug, how do we deal with that? I have no confidence.

The sponsor has several comments.

DR. THOMAS: Hi. It's actually Steve Thomas again from Celgene.

It is our experience, our received wisdom that the primary reason why the buyers' organizations are stocking the drug is that it is very hard to come by because it is not approved. It is not easily obtainable in a regulated manner. There are numerous instances in which after drugs have actually been approved that a number of the buyers' clubs have actually ceased to continue to make that particular compound available.

DR. McGUIRE: Dr. Zeldis, did you want to comment?

DR. ZELDIS: It was the same comment.

DR. McGUIRE: We're still dealing with issue 6. Are there recommendations other than the ones that we've been discussing that you would like to make at this time? Yes, Chris Mathews.

DR. MATHEWS: Just a brief comment on the neuropathy issue. I think that some consensus that we haven't achieved here needs to evolve in terms of how it is monitored, whether specific clinical examinations are recommended, and those should all be spelled out, whether physiologic testing is required and so on.

DR. McGUIRE: Yes. I think everyone is in agreement with that, and that was discussed at the meetings in November.

Obviously, the more highly technical the examination is, the less likely it is to be done well in lots of different sites, and so we were looking for simple techniques for peripheral axonal performance.

DR. SIMMONS-O'BRIEN: I'd like to ask a question. Is the renewal of the prescription the following month dependent on the patient having been seen by that prescribing physician and evaluated and examined? And if that is the case, then is that physician required then to send documentation to Celgene that they have in fact seen the patient that month and have given the go-ahead for the

continuation of the medication?

DR. McGUIRE: Are you asking the sponsor?

DR. SIMMONS-O'BRIEN: I guess so, yes.

DR. McGUIRE: Well, let me ask you. What would you like?

DR. SIMMONS-O'BRIEN: Well, I guess I would like to know that, and I'm not saying that every patient needs to be seen every month necessarily who has ENL. But I'd like to know whether it would be required -- and I think it would be a good idea to be required -- at least initially and to be modified in the future, if necessary, to have a treatment plan designed for that particular patient where the patient will undergo q 6-week or q monthly evaluation and that evaluation will include a history, a physical examination, blood work if necessary, neurologic testing again if necessary at that particular time.

I think that will benefit the patient obviously, but will also continually help us accrue data that should be meaningful because we can't begin to think that we know all about this medication and how it has worked and how it's going to affect all of these patients.

DR. McGUIRE: So, you're suggesting that we put a standard of care piece into this.

DR. SIMMONS-O'BRIEN: Yes.

DR. McGUIRE: Susan.

MS. COHEN: For better or for worse, has the Drug Enforcement Agency and Customs Service been informed of thalidomide coming into the country?

DR. BIRNKRANT: The appropriate government agencies have been informed.

MS. COHEN: Have you had any idea of what has been going on? Have they responded to you in any way?

DR. BIRNKRANT: I'm sure they're keeping the agency informed of the situation.

But I'd like to say a couple of things. If you're interested, I can elaborate on the current situation with regard to the IND process in general for those patients who don't have access either because there is no clinical trial or, as was brought out before, those patients in rural areas, patients in Alaska, et cetera, et cetera.

Because the indications today are so diverse, the agency felt that in order to ensure consistent advice to all practitioners, that they develop a thalidomide working group, and we were charged with developing some guidelines to be able to assist physicians and other health care providers about how to use this drug safely. So, the group is made up of about 20 researchers at the FDA, including legal counsel, obstetricians, immunologists,

neurologists, et cetera.

The group over time has developed an informed consent document. It's available to every health care provider who requests compassionate use thalidomide and anyone else actually who wants to look at the document.

Then we went a step further for an experimental therapy, and that is, we developed a patient education brochure which we view as a tool to the informed consent document that a patient can carry with them so that they can refer to it as frequently as they like to get the current information about how to use the drug safely.

With this program in place with regard to AIDS-related indications -- and I can speak best to those -- we currently have approximately 500 patients receiving thalidomide who are outside of clinical trials. The way the process works is that the physician or dentist calls in and requests thalidomide. Our first response is that we encourage patients to enroll in clinical trials so that the drug does get developed properly.

If for whatever reason they cannot enroll in a clinical trial, then they have to provide us with sufficient data so that we're satisfied that the patient could possibly benefit from the use of this product. In particular, we ask for the diagnosis, and in the case of aphthous ulceration, just as in the clinical trial, we want

to make sure that this drug is used for the particular indication and not something that resembles the indication. So, we ask for a biopsy report for that particular indication.

In addition, we ask for pregnancy testing in women of childbearing potential. We ask for the presence or absence of neuropathy. We are now asking about absolute neutrophil counts and we ask that physicians are aware of the recent New England Journal of Medicine article where aphthous ulcer patients were treated with thalidomide and where they did see an increase in viral load.

After that has been satisfied, we issue what's called an IND number, and that allows the health care provider to call from a list of pharmaceutical sponsors. They call and they tell them that they've been authorized by the FDA to use thalidomide. Then the paperwork continues. The drug gets shipped and records are kept.

We ask that all IRBs get informed, and subsequently we ask for progress reports on the patients. We ask for the informed consent document to make sure that the patient was adequately consented while receiving thalidomide, and we keep this in a database of regulatory information at the agency.

In addition, we have collected data on birth control methods in these women of childbearing potential,

and I can tell you that out of the 500 patients who have received it, approximately 80 of those patients have been women of childbearing potential. I can tell you that a third of those have used the birth control method of surgical sterilization, not at our recommendation, but they just happen to have had a surgical procedure.

The rest of the female patients have, at our request, used two methods of birth control, usually one hormonal, one barrier, and if there's a contraindication, we request two barriers, and we accept abstinence as a means of birth control.

The process is cumbersome not only for the patients, for the physicians, it's cumbersome for the FDA. As Dr. Woodcock was saying, if you have a standard that is for ENL, we would hope that that standard could be applied to some of the other indications as well because at present what we have is the best that we can have, given the situation, but clearly more can be done. Whatever is done for a particular indication, I would hope that it could extend at some point in time to the other indications as well so that all patients could benefit from an adequate safety monitoring program.

Thank you.

DR. McGUIRE: Dr. Orkin.

Thank you, Dr. Birnkrant.

DR. ORKIN: May I ask Debbie or Dr. Woodcock, do we know anything about these clubs -- the source of the thalidomide, for example, from Brazil or South America? Is there any overlap that's known to other sources of what's sometimes called recreational drugs?

DR. BIRNKRANT: There doesn't appear to be an overlap. Apparently the pills are not marked at all. It could be confused with aspirin, acetaminophen. They're completely unmarked, the buyers' club type of product.

DR. ORKIN: Do we actually know that in most instances that they are thalidomide?

DR. BIRNKRANT: They do get tested. It gets tested periodically.

DR. ORKIN: But we don't know the source.

DR. BIRNKRANT: No, we don't know the source.

DR. McGUIRE: We have two more issues. Let's once again focus on issue 6. Are there recommendations other than those associated with restricted distribution the committee would make regarding ways to minimize the risk and safety concerns regarding this product?

Yes, Dr. Miller.

DR. MILLER: I thought the suggestion yesterday about using an actual photo of an affected child was reasonable. The photo in here doesn't come through very well, but certainly with technology, that could be done and

that could be on every package.

DR. McGUIRE: I think that's the intention of the sponsor.

MR. WILLIAMS: It is.

DR. McGUIRE: It is.

DR. MILLER: The other question I had is in your packet I think they were 50-milligram tablets and there were 14 in a packet. Is that correct?

DR. WILLIAMS: Yes.

DR. MILLER: If someone is taking even just 100 milligrams a day, that's only a week's supply. If you're doling out packets, that would be a lot of packets to put in a drawer.

DR. McGUIRE: Fred, let's hold onto that one because we're going to talk about dosing.

DR. MILLER: Okay, I'm sorry.

DR. McGUIRE: And dosing I think is going to influence packaging.

DR. MILLER: The way they do it, okay.

DR. McGUIRE: Who is willing to walk away from item 6? Everyone?

(Laughter.)

DR. McGUIRE: Fine.

Question 7. Does the committee have any recommendations regarding appropriate dosing regimens?

What we heard from Dr. Rea was that an initial or low dose would be 100 to 200 milligrams a day I think taken in the evening and the larger dose would be 300 to 400 milligrams a day. Tom, did I recall what you said?

DR. REA: Yes, that is correct. Usually we start at 100 or 200 milligrams a day as outpatients, and because of the sleepfulness that occurs in that, I'm reluctant to go to 300 or 400 milligrams a day. I want to keep the sleepy people off the roads.

DR. McGUIRE: But you start with 100 to 200 milligrams a day in the evening as a single dose.

DR. REA: Yes.

DR. McGUIRE: And then if you increase that after the patient is accommodated to the drug or needs more drug, then you use 300 to 400.

DR. REA: I go to supplemental corticosteroids, yes.

DR. McGUIRE: Yes, Dr. Gelber.

DR. GELBER: My good friend, Dr. Rea, lives in L.A. and he hates freeways and I know he avoids them at all costs.

I use little higher doses at times. Most of the historical studies started at 300 and 400 milligrams a day, and I certainly have generally used 100 or 200. But I do see some patients that are not responding well or fully

to 200 where I do go higher. At times it's necessary to spread the dose out twice a day or three times a day, but generally a nighttime dose. But I just thought I'd give you the broad view of how it's generally used.

DR. McGUIRE: So, there is something I missed there. That the Bay Bridge is safer than the L.A. freeway?

(Laughter.)

DR. GELBER: Tom just is afraid of freeways.

DR. KILPATRICK: May I ask these clinicians, Dr. McGuire, if body weight is any consideration and how did they arrive at these magical figures which are rounded off to 00s? I'm coming at this as a nonclinician from a scientific point of view and it seems that, with respect, gentlemen, you've determined these figures from what source? Just experience presumably, but this is not science. This is clinical expertise.

DR. McGUIRE: Dr. Yoder.

DR. YODER: Just a comment about dosing. I see the patients in a hospital setting primarily, and therefore we frequently use 300 to 400 milligrams a day, usually spread out in that situation. Of course, as they respond, we will reduce it down to the lower doses.

There is no strict calculation by body weight. We do take that into consideration at times. A very small Vietnamese lady obviously would be considered for a smaller

dose. This is based mainly on experience and the past history of knowing what works primarily.

DR. McGUIRE: Dr. Gelber?

DR. GELBER: I just want to insist that we're not entirely arbitrary. Although there aren't a lot of dose comparison studies in the literature, what we generally do is use as small a dose as we can to control the systemic manifestations.

DR. McGUIRE: I think the agency wants the advisory committee to give you recommendations regarding appropriate dosing, and clearly the recommendations are going to come from the professional leprologists. And I would leave it at that.

DR. BERGFELD: I would just like to state that what was handed to us yesterday by the company suggested that the acute dosing would be 100 to 200 milligrams a day at bedtime, and for severe ENL, 300 to 400 milligrams a day at bedtime, which is not dissimilar to what has been presented.

DR. McGUIRE: Now, the question that Dr. Miller raised a few minutes ago is how the packaging should reflect the recommended dosing, and that's sort of a technical issue but it needs to be read into our activities.

Now, number 8 is really interesting. What

additional phase IV studies, if any, would the committee recommend be performed, e.g., clinical trials, pharmacokinetic studies, safety studies, special investigations?

Who would like to begin?

DR. BERGFELD: I would. I have an opinion on this. I believe that the phase IV study that is in the Philippines should be finished. That's of utmost importance, and the data from that should be synthesized and hopefully this committee might see it, but realizing that we may not be the end group to make this decision.

Under the pharmacokinetic studies, I strongly believe we have to understand more about the metabolites, the elimination, and the storage of this drug. Specifically in that area, one might be looking for a metabolite that would work better with less of the side effects as has been stated today.

Under the safety studies, there's no doubt in my mind the neuropathy has to be better worked out and recommendations for safety monitoring of patients who take this drug need to be put in place. I will just say that and quit.

DR. McGUIRE: I would like to say something. I'm not speaking for the sponsor, but I would guess that the sponsor would like to have a better product than

thalidomide. They would like to have a product with the efficacy and without the toxicity. If I'm wrong, tell me.

DR. THOMAS: You're not wrong, sir. You're absolutely right. It's actually Steve Thomas again.

As I alluded to all those many years ago -- actually yesterday morning -- our company is actively involved in the development of a range of analogs and derivatives of this compound which are being used to explore actually both the unique mechanisms of action of the parent compound, to provide us actually with extra information which will enable us, hopefully, to retain efficacy in specific indications, having engineered out a range of toxicities, obviously the most important of which is birth defects.

That's not simple. That's the holy grail of drug development. It isn't actually going to happen overnight. It is actually something which our company is completely committed to. It is the future of our company, and there is nothing that -- our company and me personally would like to be able to provide to this advisory committee in the future is the successor actually to this compound.

DR. McGUIRE: I'm not surprised at what you said, but I'm still very happy to hear you say it.

I think what all of us would like to learn through your efforts is what the target was in the first

place because I think we don't know how the drug works. It's very likely people who are in your kind of business who will discover that.

What else would we like the sponsor to do in the next several years? Susan.

MS. COHEN: It's more the packaging. Are home pregnancy tests going to be considered pregnancy tests, or is that going to be excluded? Are these things expensive for people to do since you talked about the socioeconomic class of the people who are using thalidomide? But I think you have to. If you don't want home pregnancy tests, you're going to have to say that it has to be done at a certain, specific place.

MR. WILLIAMS: Yes, Ms. Cohen. We recognize that it is important that these tests be administered in a professional setting. We've had some discussion with the agency and I know the agency is seeking advice from other sources, including the American College of Obstetrics and Gynecology, as to the most effective and most practical forms of pregnancy tests. We expect that in the final labeling that will be reflected.

DR. McGUIRE: Other comments from the committee? Dr. Miller.

DR. MILLER: I would just like to bring up an issue that Dr. Duvic brought up yesterday about the name,

that she had a concern that Synovir sounded like another antiviral. And should the name be thalidomide or how would that be used? That certainly should be discussed.

DR. McGUIRE: Yes. We discussed that at our November meeting. I felt very strongly that to some degree, foolishly, that thalidomide should be in big letters, and someone pointed out to me that I was practically the only one in there who knew what thalidomide really was because everybody else is of an age that they came on the scene after thalidomide. So, it's not the brand name that we'd like for it to be.

Nonetheless, I think there was a consensus that thalidomide should be associated with any other name that's used for it and there shouldn't be a whole family of names. It should be very distinctive, very straightforward.

Now, the question is its similarity to an antiviral, and I don't know how the sponsor wants to deal with that. It does sound like it ought to be good for HSV.

DR. WEINTRAUB: Dr. McGuire, the company has been informed some weeks ago that the Nomenclature Committee had reviewed the rame and not found it the right name to be used.

DR. McGUIRE: It's the right name for another product.

(Laughter.)

DR. WEINTRAUB: Perhaps.

DR. KILPATRICK: Dr. McGuire?

DR. McGUIRE: Yes, Jim.

DR. KILPATRICK: Following on Dr. Weintraub's comment and indeed to indicate my confusion, I'd like some clarification of where we are. We started off with a set of questions from FDA which were specific to Synovir. We proceeded to delete the word "Celgene" in front of thalidomide, so we were talking about generic thalidomide. But we now appear to be talking as though we had already voted to recommend approval for Synovir as opposed to thalidomide by this company. Can you clarify what the situation is?

DR. McGUIRE: Well, this sponsor is interested in Synovir and this committee is interested in thalidomide. We asked the agency if we could drop the Celgene as a modifier of thalidomide.

DR. LUMPKIN: Dr. McGuire, do you want me to speak to that from our perspective?

DR. McGUIRE: Please.

DR. LUMPKIN: I think people need to remember from the agency perspective what we needed from the committee today was a basic medical policy kind of perspective. Here the drug thalidomide -- and perhaps we ought not to say the generic drug thalidomide. That takes

us down a whole other road. The general term for the drug thalidomide is one obviously that has a tremendous amount of baggage and it has a tremendous history that we've all talked about the last two days.

What we needed from the committee here was a perspective from the medical community of are we in 1997 at a point where, in the treatment of ENL, you feel that the benefits outweigh the risks, and I think we got that message from you as clinicians.

I think people need to remember that generally, no matter what it is, when we come to a committee, even though the questions are often worded "would you approve such and such product," you generally only look at the clinical implications of it. We, for example, don't bring manufacturing issues up, but the manufacturing procedures are part of the marketing application. When we, at the end of the day, have to make the decision, we have to make the decision on not only whether the clinical data support the use of the product, but whether the company can manufacture it and several other different things that come into it.

What we did not want to have happen today was for people to somehow confuse Celgene's thalidomide with the basic issue of thalidomide, which is what we wanted to get from you, and I think we did get that today. At least that's what I'm taking away from here.

Joe, is that a fair expression from your perspective as Chair?

DR. McGUIRE: I wouldn't have said it so well, but thank you.

(Laughter.)

DR. McGUIRE: I think we've just fallen off the end of question 8 unless there is more to be added to question 8.

DR. WOODCOCK: Is the committee member's question satisfied, however, around Celgene thalidomide versus thalidomide?

DR. KILPATRICK: I'm very disturbed because I came prepared to answer the specific questions. In mid-field the questions were changed. I accordingly changed some of my recommendations, and as I've indicated, I don't know what this committee's recommendation to the FDA is now because I came to speak to a specific product being produced by a specific company and now I'm talking about something which will go back to historical data, to clinical experience, et cetera as opposed to the evidence put forward by a company specifically on their product. And those two things are quite distinct in my mind.

DR. WOODCOCK: I think if you have opinions you'd like to contribute on that bridge between the historical data and the particular data on Celgene's