CENTER FOR DRUG EVALUATION AND RESEARCH

FOOD AND DRUG ADMINISTRATION

FORTY-SEVENTH MEETING

OF THE

DERMATOLOGIC AND OPHTHALMIC DRUGS ADVISORY COMMITTEE

8:36 a.m.
Thursday, September 4, 1997

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

APPEARANCES

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CELGENE REPRESENTATIVES:

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DAVID R. CORNBLATH, M.D.
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STEVE THOMAS, PH.D.
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JERRY ZELDIS, M.D., PH.D.

ALSO PRESENT:

CHRISTOPHER J. DOYLE
JAMES W. HANSON, M.D.
LEWIS B. HOLMES, M.D.
LYNN M. KLEIN
CYNTHIA PEARSON
VICKI WALTON

C O N T E N T S

C O N T E N T S (Continued)

C O N T E N T S (Continued)

P R O C E E D I N G S

(8:36 a.m.)

DR. McGUIRE: This is the 47th convening of the Dermatologic and Ophthalmic Drugs Advisory Committee meeting of the Food and Drug Administration.

By the close of business tomorrow afternoon, this committee should have given the agency some recommendations on their evaluation of efficacy and safety of thalidomide. Thalidomide has played a very important role in the development of standards of the agency, and these should be very interesting discussions.

I would like to turn the meeting over to Tracy Riley for the conflict of interest.

MS. RILEY: Good morning. Welcome to the meeting.

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 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 fairness, that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

Also there are four special government employees who are granted temporary voting status today to participate in this meeting: Dr. Wilma Bergfeld, Dr. Ken Hashimoto, Dr. Fred Miller, and Dr. Eva Simmons-O'Brien.

And for the people at the table, there are additional review materials in your packet that you had not received before.

Thank you.

DR. McGUIRE: There will be introductory remarks from the agency, but before we hear those, I would

like to start with the left end of the table and have people sitting at the table introduce yourself, please.

MR. WARREN: I am Randy Warren from the Thalidomide Victims Association of Canada.

DR. SHANNON: My name is E.J. Shannon, from the Gillis Long Hansen's Disease Center in Carville, Louisiana.

DR. CRAWFORD: I am Colin Crawford, from the London Imperial College, School of Medicine.

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

DR. MATHEWS: Chris Mathews, University of California, San Diego, and member of the Antiviral Advisory Committee.

DR. DUVIC: I am Madeleine Duvic, from Houston, Texas, M.D. Anderson and UT. I am a dermatologist.

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

DR. ORKIN: Milton Orkin, from the University of Minnesota, Minneapolis, Minnesota.

DR. BERGFELD: I am Wilma Bergfeld, a dermatologist from the Cleveland Clinic.

DR. McGUIRE: I am Joe McGuire, from Stanford University, dermatology and pediatrics.

MS. RILEY: I am Tracy Riley, the Executive

Secretary to the committee.

DR. SIMMONS-O'BRIEN: I am Eva Simmons-O'Brien, from the Departments of Dermatology and Internal Medicine at Johns Hopkins in Baltimore, Maryland.

DR. KILPATRICK: I am Jim Kilpatrick, School of Medicine, Medical College of Virginia, Virginia Commonwealth University, biostatistician.

MS. COHEN: I am Susan Cohen, and I am the consumer member.

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

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

DR. BIRNKRANT: I'm Debra Birnkrant, acting Division Director, Division of Antiviral Drug Products, and I chair the Thalidomide Working Group at the FDA.

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

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

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

MS. PENDERGAST: Mary Pendergast, Deputy Commissioner, Food and Drug Administration.

DR. McGUIRE: Thank you very much.

The first remarks will be presented by Mary Pendergast.

MS. PENDERGAST: Good morning. And thank you for coming to our Dermatologic and Ophthalmic Drugs Advisory Committee meeting.

I would like to especially thank the Chairman and the other members of our advisory committee, who give so generously of their time and their expertise to the FDA.

We are here so that our advisory committee can review Celgene's new drug application for the use of thalidomide for the treatment of erythema nodosum leprosum, abbreviated as ENL, a complication which occurs in a subset of patients with Hansen's disease, also known as leprosy.

Last November we brought to this advisory committee our concept that thalidomide, despite its history and known risks, could be an approvable drug. We believed, and still believe, that thalidomide may have the capacity to treat as well as to damage. We also explained why we felt we needed to change the medical landscape when it came to thalidomide.

Because thalidomide was not approved, patients with Hansen's disease were getting substandard drugs that were not manufactured under good manufacturing practices. And although thalidomide held out promise for other

diseases, there were no well-planned schemes for studying the drug for other diseases.

The Health Resources Service Administration was running out of money to pay for the distribution of the drug under investigational new drug exemptions.

And we were concerned about the proliferation of groups that were distributing bootleg, illegal thalidomide to patients with AIDS and cancer, without careful controls that would have prevented birth defects.

Consequently, we took several steps to change the landscape. One step was to encourage companies to pursue approval for diseases for which there might be the requisite data. Celgene took up that challenge and has pulled together an application for the use of thalidomide for ENL, an indication for which the drug has been used for over 30 years.

We also stopped the illegal distribution of thalidomide through buyers' clubs. Several clubs agreed voluntarily to stop distributing thalidomide. And we stopped the remaining buyers' clubs' activities through legal proceedings.

We have also collaborated with the National Institutes of Health and the Centers for Disease Control to design a two-day public scientific meeting, that will be held next week, to explore whether and how thalidomide

could be used for other clinical uses. We know that thalidomide is being studied as a treatment for many serious diseases, including ENL, chronic graft versus host disease, cancer, and HIV infection.

This meeting will discuss the advances and research opportunities of thalidomide in the treatment of various disorders.

But next week's meeting will have a broader focus as well. We need to remember that more than half of the population alive today was not yet born when the thalidomide tragedy took place. There are many in our society, patients and physicians alike, who do not know the thalidomide story. Thus, as an education to some and as a reminder to others, we will also discuss the past uses of thalidomide, the risks associated with thalidomide and reproduction, the legal, ethical, and other public policy concerns surrounding thalidomide's use, and the management of the adverse effects of thalidomide.

This will be an important and useful meeting, and the results of that meeting, as well as your expert advice today, will be taken into account before FDA makes any decision on the approvability of thalidomide for ENL or any other disease.

I know that there are some who wish that next week's meeting could have been held before this meeting.

But scheduling difficulties made that impossible. In my view, though, it shouldn't matter. For today, we are attempting to have an ordinary advisory committee meeting.

What we would like today is for the advisory committee to assist us with their expertise on the particular new drug application that is before them, and help us answer the question of whether thalidomide is effective in the treatment of ENL, and whether the steps that have been proposed to control the distribution and use of the drug will permit thalidomide to be considered safe under that scheme.

Although these are the normal, straightforward questions we ask of advisory committee members all the time, they will be harder answers to come by today because, as you have seen, this is not a fully conventional data set. Celgene did not invent thalidomide and then develop the drug through conventional studies. Rather, thalidomide has been used for ENL for over 30 years without the rigorous collection of data one would expect from real clinical trials.

Therefore, it is critically important to us that you give a careful and thoughtful look at the data that does exist, and help us decide whether thalidomide should be approved as a treatment for ENL. This will be challenging, but very important efforts, and we look

forward to hearing your deliberations.

So, I would like to thank you again for being a member of our advisory committee, for helping us out on this very tough question. Thank you again for your attention.

DR. McGUIRE: Thank you, Ms. Pendergast.

Dr. Weintraub.

DR. WEINTRAUB: Thank you, Dr. McGuire.

Several people have asked, since we've distributed signed reviews, stating the reviewers' conclusions on the approval of thalidomide, why are we having an advisory committee meeting? And the question of people who oppose it, they said, well, you have already made up your minds; it is a closed issue. Well, I assure you that it is not.

Let me tell you a little bit about the procedure at FDA. We believe that in a science-based enterprise, which this is, everyone is entitled to their own interpretation of the data -- particularly people who have worked very closely with the information coming from clinical trials or coming from studies such as these data sets, as Mary just pointed out. They are not always conventional data sets.

But we do not demand that everybody has to have an opinion that is totally in concert with other opinions

and other points of view. We believe in the value of ideas and of insights.

Now, there are many reasons why a particular reviewer can come to a different judgment. The primary reviews are often completed earlier in the final approval process. And the reviewer may not have a total picture of the final plans -- for example, in this case, such as restricting distribution -- and perhaps, in that sense, altering the risk/benefit relationship.

Of course, with a controversial drug such as thalidomide, there are bound to be differences of opinion. The outlook of everybody may be different when the drug is so controversial. Several people, all acting in good faith, can look at the same numbers, the same dots on a graph, and come to different conclusions. This is especially true if the numbers and dots come not from clinical trials but from experiences that were never intended to be interpreted as if they came from double-blind, randomized, carefully controlled experiments -- for example, things like the information from the clinical care of patients -- even those who are carefully followed.

In the FDA, we have a system of supervisory oversight. That is why we have given you primary and secondary reviews, the Division Director's opinion and the

Office Director's view. In some cases, we have the Director of the Office of Review Management over the Office Director, and the Center Director as well.

Except for the primary reviewer, we can all write overriding memoranda. I know that my colleagues -- the other four office directors -- and I take overruling our trusted colleagues and coworkers very seriously. It is not something we do lightly. Instead, the decision involves delicate balances and inner struggles.

So, although you have primary and secondary reviews and a Division Director's memo in your packet of materials, I will assure you that our minds are not made up and we are not done yet. Our analysis has not been locked in one way or the other.

We invited you here because we respect your judgment. Even if we do not take your advice, as occasionally occurs, we still learn from your discussions, from your unique points of view, your questioning of the presenters, and your deliberations over the questions.

Now, I am sure that we will still learn from your deliberations over the next day and a half, and I am certain that we will receive the benefit of your advice. I appreciate it, and I know actually the entire FDA is really in your debt for doing that.

Thank you.

DR. McGUIRE: Thank you, Dr. Weintraub.

I conclude from what you have said that this is not a stacked deck.

DR. WEINTRAUB: That is correct.

DR. McGUIRE: Let's go on to the public hearing. There are two statements to be read.

MS. RILEY: The first statement is from the Office of the Executive Director of the American College of Obstetricians and Gynecologists.

On behalf of the American College of Obstetricians and Gynecologists, ACOG, an organization representing 38,000 physicians dedicated to improving the health care of women, ACOG does not believe that thalidomide, nor any drug, should be kept from being introduced or withdrawn from the market solely because it may be teratogenic. We strongly support efforts to prevent exposure of women who are pregnant or contemplating pregnancy from known teratogenic agents.

Sincerely, Ralph W. Hale, M.D., Fellow of the American College of Obstetricians and Gynecologists.

The next statement is from the Leonard Wood Memorial American Leprosy Foundation.

I, Dr. Gerald P. Walsh, Scientific Director of the American Leprosy Foundation, am submitting a written presentation on behalf of my organization in support of the

licensing of thalidomide. I regret that at the time of the meeting it was necessary for me to be at our research facility in the Philippines.

Founded in 1928, the Foundation conducts, maintains and supports laboratory investigations, clinical studies and related research, with the ultimate goal of eradicating leprosy. We also disseminate information about the source, diagnosis, treatment, and prevention of the disease, just as we voluntarily aid, establish, maintain, and support clinics, hospitals, and laboratories for diagnosis and treatment of the disease. The Foundation is headquartered in the United States, and maintains a leprosy research center in Cebu, Philippines. The Center is staffed by 34 individuals, composed of professional as well as technical and support staff. It is in Cebu that our scientific research is carried out. The Foundation is foremost among many American agencies in this field, and we are proud of the many achievements and contributions we have made that we believe will eventually lead to the eradication of this tragic disease.

Few diseases are as feared and misunderstood as leprosy. Since pre-Biblical times, the leprosy patient has been surrounded by myth, superstition, fear, apathy, and rejection. Some progress has been made toward changing these attitudes, but unfortunately they are still prevalent

in many parts of the world, including the United States.

Contrary to popular thought, leprosy remains a major health problem in many developing countries, with more than 600,000 new cases detected annually. Today it is most prevalent in tropical and subtropical climates, but was rampant in temperate climates until the late 19th century. Of concern to this committee are the approximately 6,000 known cases of leprosy in the United States. The actual number of cases is undoubtedly higher, and climbing, in light of sustained immigration from Third World countries to the United States.

Leprosy is currently treated with a combination of drugs. Although multi-drug therapy is the treatment of choice, serious problems still remain. New drugs are needed and research must continue.

Up to 30 percent of all people afflicted with leprosy suffer from erythema nodosum leprosum, ENL, an acute reactional phase from leprosy that is very painful and debilitating for patients. It usually occurs after treatment is started and is characterized by the appearance of tender nodules, accompanied by fever and joint pain. In severe cases, the patients are bedridden for weeks. And some of these develop chronic ENL, which incapacitates a patient permanently. ENL is thought to be immunologically mediated, but the specific factors that precipitate

episodes of ENL are not clearly understood. Recent studies have suggested that cytokines may play a key role in ENL.

We at the American Leprosy Foundation are proud to have pursued research that addresses the key questions still surrounding the etiology and treatment on leprosy and ENL. We are very concerned that in our clinics today we can offer patients only a limited number of treatment options appropriate to their medical needs. This, of course, includes thalidomide, which the World Health Organization has determined is standard of care for the treatment of ENL.

We recognize that thalidomide is restricted in that it cannot be used to treat pregnant women or, for that matter, women of childbearing age. But for the appropriate groups, it has the potential for enormous good in leprosy patients who develop ENL. In the words of the International Federation of Anti-Leprosy Associations, it is very effective for controlling ENL.

Our studies in Cebu, Philippines, that are partially supported by Celgene Corporation, have shown the remarkable effect of thalidomide and represent an important treatment option for patients living with ENL. We at the American Leprosy Foundation urge you to recommend approval of this drug.

Thank you.

Gerald P. Walsh, Ph.D., Scientific Director.

DR. McGUIRE: Thank you, Ms. Riley.

We will have an oral presentation now from Dr. James Hanson. Dr. James Hanson is representing the American College of Medical Genetics, the American Academy of Pediatrics and the Academy Committee on Genetics.

DR. HANSON: Mr. Chairman, members of the committee, I am James Hanson, Professor of Pediatrics at the University of Iowa. I am here representing the American Academy of Pediatrics, as you have heard.

It is not without reason that thalidomide has been termed the most notorious human teratogen. The drug was introduced in 1956 in West Germany, as an effective sedative and hypnotic. It was also used to treat nausea and vomiting in pregnancy. By the end of 1961, thalidomide, sold under 51 different brand names, was identified as a human teratogen and removed from the market. More than 10,000 infants worldwide were born with malformations attributed to the use of thalidomide in pregnancy. In 7 of the 17 cases reported in the United States, the thalidomide was purchased in another country.

And I might add parenthetically that the avoidance of a similar tragedy in the United States was largely due to the efforts of Dr. Francis Kelsey, who is sitting over here on my left.

(Applause.)

DR. HANSON: The mechanism for teratogenicity of thalidomide is still not known. However, the period of greatest sensitivity appears to be between days 21 and 33 of gestation. It is of great concern that the effects of thalidomide on the fetus do not appear to be dose-related, and teratogenic effects appeared in over 80 percent of the fetuses exposed during the critical period.

Thalidomide produces major malformations of the upper extremities, ranging from missing thumbs to missing radii to absent ulnas and humeri, including so-called phocomelia and the micromelia. It sometimes produces major malformations of the lower extremities as well. In addition, fetuses exposed to thalidomide can have congenital heart defects, craniofacial anomalies, facial palsies, urogenital anomalies, and a number of other structural birth defects. Concerns have also been raised about associated developmental disabilities.

While available research supports thalidomide's effectiveness in the treatment of leprosy, graft versus host disease, aphthous ulcers, wasting in AIDS patients, and several other disorders, use of this drug comes with great risk to the fetus.

The American Academy of Pediatrics is deeply concerned about the approval of this drug in light of its

known teratogenic effect is. Despite any attempts to educate and monitor patients and to preclude the use of thalidomide during pregnancy, some fetal exposures will occur. The committee should realize that infants will be born with preventable birth defects if this drug is approved for prescription use. The experience concerning Accutane use is revealing. Even with a strong education program, some 40 percent of the women of childbearing potential who took Accutane did not have a pregnancy test before initiating treatment.

For a drug like thalidomide, that has a high rate of teratogenicity, a 40 percent noncompliance to warnings about use during pregnancy could result in a significant number of affected infants. This is particularly true if thalidomide is used by women who are infected with HIV, many of whom, because of problems with drug abuse or low education or other risk factors, will be less likely to be compliant with complex regimens.

It is the opinion of the American Academy of Pediatrics that thalidomide be a restricted drug, available only for indication through a single national resource, subject to public oversight. At the very least, the American Academy of Pediatrics believes that the use of thalidomide should be restricted to those disorders for which it has been shown to be effective in clinical trials

and for which other therapies are not available or have been unsuccessful. Since thalidomide would rarely be used for emergency medical treatment, documentation of negative pregnancy testing, two means of contraception and educated, informed consent should be required before this drug is given to a premenopausal female.

We certainly recognize the potential effectiveness of thalidomide in a number of clinical areas, and the benefits of the drug to some patients. However, even with a massive educational program and adherence to strict guidelines, it is clear that the general licensing of this drug will come with an increase in devastating birth defects, even if effective guidelines are followed. It cannot be too highly stressed that these birth defects will result in physical, financial, and emotional costs to affected children and their families, and that additional burdens will be incurred by society.

In closing, the American Academy of Pediatrics urges this committee and the FDA to seek and heed the advice of all organizations whose focus is the health and welfare of America's children before considering the approval of thalidomide. If the FDA is to approve this dangerous drug, the committee needs to determine appropriate and necessary safeguards to minimize the risks to future children.

Thank you.

DR. McGUIRE: Thank you, Dr. Hanson. And thanks to the Academy for that well worked out statement.

We have one more oral presentation from Anne Pasturzak, representing Mother Risk.

(Pause.)

DR. McGUIRE: Absent Ms. Pasturzak, we will go on to the scientific presentations by Celgene. Dr. Steve Thomas will tell us about the chronology and pharmaceutical development.

DR. THOMAS: I'm Steve Thomas. I welcome you all.

I think the first thing I should say is that our company is in the debt of the advisory committee and also the FDA in having an opportunity, as of this date, to make some formal presentations to you. Although this is, and we hope it will be, an ordinary advisory committee, I'm afraid I cannot regard it like that. I think obviously this is very important from our company's viewpoint. However, it is of more general import than that.

I personally am actually 36 years old. And I actually recognize that it was fate that allows me to be speaking here with one perspective and actually not with another perspective.

With that in mind, I would just like to lead on

to the reason why we are here. Yes, the reason why we are here is to seek your guidance, to hear your views, to express our views on the efficacy and safety of this interesting, unique compound in the treatment of ENL and leprosy.

I would like to ask you, if you have any specific questions that you would like to pass on to representatives of our company, I may be able to help you in actually directing those questions.

I think it is useful to try and explain how our company has established its interest in ENL and to put that into a time line and a chronology and also in a perspective of what the company is involved with in other areas. Initially, we became aware of the use of the drug in ENL through an evaluation of the literature, the previous human use of the drug, in support of an AIDS-wasting IND that was entered into the FDA in January of 1994.

During that literature overview, it became apparent that there was very extensive previous human use experience of the drug in ENL and leprosy. Most notably, our company became aware of a substantial database, which spans over 18 years of use, which is held at the Hansen's Hospital in Carville, Louisiana, and continues to acquire data on the use of the drug under an IND that is authorized -- IND 11,359 -- actually by the FDA.

It's also interesting, I think, to note a way in which, the authorization of the IND came into existence. It was actually based on the substantial earlier clinical experience which identified the potential use of the drug in this ENL indication.

I think it is also actually very important that our company points out and agrees with the views which have already been established by Mary Pendergast, that because of the way in which our company has identified data, you will be asked to give your critical opinion on a variety of historical data sets as well as information which is more current from ongoing studies which our company is running in the Philippines.

These historical data sets are not providing, even from a company's viewpoint, an NDA which is ideal in form or content. I would ask the members of the committee, when they are making their deliberations, to please actually take in context that ENL is an orphan indication, where access to individuals, patients who are available to enroll in clinical trials in the U.S. is very limited.

However, with all of the caveats as I have just identified them, our company would like to try to persuade you that it is clear that in the variety of data sets efficacy of the drug has been established, and we believe that the drug can be safely used in this indication.

I must allude also to the comments of Mary Pendergast again in identifying how our company's interest in this indication intensified. As the FDA has already told you, they invited interested industry sponsors of INDs to a meeting in November 1995, where it became apparent that the agency had concerns over the potential use of unregulated drug sources, specifically in the AIDS area.

At that meeting, it was also pointed out that due to the interest in the evaluation of the drug, there was increasing compassionate use needs which were escalating at a very rapid rate and that FDA was keen to try to obtain from sponsors reviewable NDA submissions so that this particular range of circumstances could actually be turned into a more controllable and regulated outcome.

Coincidentally, at that moment in time, as you have already heard, the availability of drug through the Hansen's Hospital IND for emergency uses other than Hansen's, or other than actually for Hansen's patients, had to come to an end. Our company interpreted that as providing an urgent need for consistent, high-quality availability of drug manufactured in compliance with the FDA's own guidelines on good manufacturing practices, and our company at that moment in time actually made a commitment to make our drug supplies available to these other emergency use IND indications.

I think it is important that I actually put our ENL indication in context. Our company is committed to the intensive clinical evaluation of this drug in a number of life-threatening indications. AIDS wasting, aphthous ulcers and graft versus host disease you have already heard about. I think it is also worthwhile actually pointing out that as of this date, as a result of our company's efforts, we have, where authorized by the FDA, actually made our drug supplies available in over 500 emergency use INDs, both in the United States and also in Canada, and that this provides very useful information on the exposure of the drug and the safety of the drug.

Lastly, I would just like to point out that our company recognizes that there are severe problems associated with the use of this drug. However, there are also unique opportunities of efficacy which have actually been identified previously, will be discussed during this forum, and also at the open meeting next week. We would like to seek to identify, to understand the mechanisms through which the parent compound is providing efficacy whilst trying to engineer a reduced and changed profile of toxicities. And this really our company's long-term goal.

With that long-term view in mind, which I think is a laudable and praiseworthy goal, our company is now in the position to take an analog of the parent drug

thalidomide into healthy human volunteer studies actually later this month.

Lastly, I would like to just introduce over the course of the meeting our company's outline and plan overall for speakers and presentations. It is in a slightly different order to that which you have on your agenda. The first speaker, who is going to address issues of PK and metabolism is Dr. Wayne Colburn of MDS Labs, which is a clinical research organization, which has undertaken the vast majority of our work in this area. And I will actually just pass it over to Wayne.

DR. COLBURN: Good morning, ladies and gentlemen. I appreciate the introduction. And I would like to expand on that a little bit.

I work for MDS Harris Laboratories, which is a contract research organization, and I have also been working with Celgene over the last two or more years in assisting them with the development program that we are going to talk about today. MDS Harris has been involved in working with Celgene to design and conduct the clinical studies, as well as to assist in the interpretation and reporting of that data.

What I want to talk with you about this morning are some of those outputs. In addition to the initial three clinical studies that were presented in the data

package, there are four additional studies which we'll also briefly take a look at this morning.

Could I have the first slide, please?

The first three studies listed on this slide were presented in the original data package. And essentially, this is a summary that gives the study number or protocol number, the population studied, the number of participants, broken down by number of male subjects and number of female subjects. It also provides a very brief overview of the design and what dose or doses were used.

In the first study, PK-001, we looked at healthy volunteers to assess the bioequivalence of two Celgene lots, as well as a Tortuga lot, to determine whether the proposed commercial dosage form was bioequivalent with the dosage forms that were used in clinical trials, as well as to look at a lot that had been evaluated in ENL in previous years.

The next study looks at healthy volunteers, again, single dose, to evaluate dose proportionality of subjects, looking at doses up at 200 milligrams.

Then the other study that was in the original package was actually a study conducted in a small group, two men and four women, with Hansen's disease. This was a single-dose study, which was intended to look at the pharmacokinetics in that patient population as well as to

look at the metabolism of thalidomide.

Now, subsequent to that submission, we have conducted additional studies. And those I will go over briefly here. PK-006 is also a study in healthy volunteers. There were 13 study participants, of which 5 were male and 8 were female. This was a single-dose bioequivalency study to look at the effect of food on the bioavailability of the Celgene product, as well as to look at another lot of material manufactured outside of the United States.

Another study, PK-UK001, was conducted in HIV-positive subjects. 16 participants, all male, participated in a dose-proportionality study which looked at doses of 100 and 200 milligrams.

I might mention back here that this study, in fact, has doses that range from 50 to 400.

Two additional studies which are put into another category -- all of the previous studies were single-dose in nature -- looks at multiple dosing. There were two studies in that that have those characteristics, the first one being PK-003, conducted in healthy female volunteers -- 12 females -- which received single doses.

This is somewhat of a misnomer. It really looks at the single-dose and multiple-dose thalidomide pharmacokinetics. In addition, a single dose of Ortho

Novum, a commonly used oral contraceptive was administered after thalidomide had been brought to steady state, or on day 21. And essentially, we looked both at the accumulation of thalidomide, or the effect of repeated dosing on thalidomide, as well as the effect of thalidomide on an oral contraceptive in this study.

Then, finally, we did a multiple-dose study in Hansen's disease patients -- 4 -- due to the small numbers of patients available -- 3 of which were male, 1 of which was female. And here we looked at the steady state pharmacokinetics in doses that was what these people were receiving during their normal therapy, which ranged from a single, daily 50-milligram dose, up to 300 milligrams given in a t.i.d. regimen.

Now, let's evaluate, or take a quick overview of, some of the data that resulted from these studies.

First, one study that was not listed on the previous slides is we also looked at the in vitro human metabolism of thalidomide. And this was done in human liver microsomes. It's shown here. And what it showed was that, in fact, the human liver microsomes did not metabolize thalidomide to any appreciable extent. What this would suggest, then, is that the predominant change or apparent metabolism of thalidomide is a function of simple hydrolysis.

In addition to this, one of the concerns was that thalidomide could either be induced or inhibited itself by other drugs or could cause the induction or inhibition of other drugs. In support of that question, we provide the following information.

We looked at a series of cytochrome P450 isozymes, and in no case was there any evidence of inhibition or induction for CYP 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, and 3A4. And these are the enzymes that are most commonly associated with drug metabolism. So, we don't anticipate that there will be any impact of thalidomide on other drugs or any effect of other drugs on the metabolism of thalidomide.

Now, to go through the studies that we talked about briefly before, or gave the outlines for. The basic take-away messages for these single oral-dose studies was for a 200-milligram dose, the oral absorption, or apparent absorption, half-life is 1 hour, based on this data as well as others. In reality, this is probably the elimination half-life.

The apparent elimination half-life is approximately 5 and a half hours. And as we will see from other data that I'll show later on, in fact, this is probably the absorption half-life in what kineticists would call a flip-flop model. And this is true not only in

healthy volunteers but in HIV-positive subjects that we studied.

Looking in healthy volunteers at the 50- to 400-milligram dose range, there is dose proportionality with respect to the area under the curve. In fact, the extent of absorption is the same from 50 to 400 milligrams. However, Cmax does not increase proportionally due to delayed absorption or prolonged absorption between the 200- and 400-milligram dose. How that evidences itself is, again, the apparent elimination half-life, which we believe is truly the absorption half-life, changes from 5.5 to 7.3 hours between 200 and 400 milligrams.

Again, back to the 400-milligram dose level, but, in this case, looking at patients with Hansen's disease, the pharmacokinetics are similar when dose-adjusted back to the 200 milligrams, and also compared to the 400 milligrams here, to all of the pharmacokinetic profiles that we observed in healthy volunteers. So, the overall message there is that the pharmacokinetics in Hansen's patients is similar to that which we see in healthies.

The other observation was that absorption and elimination half-lives were somewhat longer at this 400-milligram dose.

Taking this to the next step, they are similar,

as we stated before. And the absorption half-lives were somewhat longer, but the metabolism that we observed in vivo is essentially confirmed in this 400-milligram dose study in Hansen's disease patients. In fact, the three metabolites that would be anticipated to be formed were not observed in the plasma of these subjects. Less than 1 percent of the dose was excreted intact in urine, and even a lesser extent, less than .1 percent of the dose, was excreted by one of the hydroxy metabolites, 4-hydroxy-thalidomide.

Finally, to get back to the bioequivalency issues from the single-dose studies, Celgene's proposed commercial formulation is bioequivalent to their formulation that was used in their clinical studies.

However, the Tortuga lot, a lot of material, or a manufacture of material, that has been used extensively in the treatment of Hansen's patients having ENL, was not bioequivalent to either of the Celgene formulations.

The extent of availability was identical. The areas under the curve were identical for the two products. However, the Cmax for the Tortuga lot was about one-half that for the Celgene lots.

I think this is the final single-dose overview slide, and it looks at the effect of food on the pharmacokinetics of thalidomide. And, in fact, there is no

change in the area or the extent of availability, but there is a slight delay in the absorption, and this results in a delay in Tmax, or the time of the peak concentration after a single dose.

Now, we'll move on to the multiple-dose pharmacokinetic information. Again, the first set of data has to do with Hansen's disease patients. We see, using the multiple-dose data, that, again, the pharmacokinetics in Hansen's disease patients is similar to that observed in healthy subjects.

Also, supporting the single-dose study at the 400-milligram dose, the purported metabolites, again, were not measurable in plasma, and only less than 1 percent of the daily dose was excreted in urine. And only approximately 0.2 percent of the dose was found in urine as the 4-hydroxy metabolite. Neither of the other two metabolites that we looked for were observed.

The final multiple-dose study is shown here. The results from that study. When thalidomide was administered to women over 18 days, the pharmacokinetics were similar between day 1 and day 18, indicating only a slight accumulation of drug during that period. That's consistent with repeat-dose studies in male healthy volunteers as well.

In addition, when a single two-tablet dose of

Ortho Novum oral contraceptive was administered, the pharmacokinetics of the ethinyl estradiol and the norethindrone from that product was not altered by the 21-day administration of thalidomide.

The other observation was that, during the 18 days of dosing, the pharmacokinetics of thalidomide did not change in premenopausal women.

Now, just to come back to the take-home messages from this significant amount of data that I have tried to present in a short period of time, I'll try to briefly summarize what I think the take-home messages are.

One of the things that has been a concern is the lack of equivalence between the Tortuga lot and the Celgene lot, because some of the data that will be presented later today, the Tortuga lot was used.

If, however, we take the data that was generated from that pharmacokinetic study and simulate what steady state conditions would be -- the concern had been that Cmax was lower by about one-half that of Celgene -- on repeated dosing, because of the difference in the apparent elimination half-life, in fact, Cmax, in the areas under the curve, will be very similar at steady state.

Secondarily, gender. Female subjects composed 26 of the 83 subjects that were studied during these clinical trials. Both females and males exhibited very

similar pharmacokinetic profiles. So, gender is not an issue, and this was true not only on single doses, but at steady state.

Looking at the patient populations, the patient population of interest here, obviously, is ENL. And we have shown that although there are slight differences on single dosing in ENL patients, that in fact on both single dosing and multiple dosing, the pharmacokinetics are similar to those observed in healthy volunteers.

Then, finally, to close, with the in vitro and in vivo metabolism that was conducted here, we have shown that there should be no concern for potential interaction of thalidomide with rifampin, dapsone, or any other treatments that are commonly used in Hansen's disease patients based on the data that we have provided today. And we have shown conclusively that there is no interaction with oral contraceptives.

I'd like to thank you for your attention, and then our next speaker. Thank you very much.

DR. McGUIRE: Let me question the sponsor. Would you like for the committee to ask questions during the presentations? Or we can hold questions until the end.

DR. THOMAS: If you would feel more comfortable asking the questions when they are fresh, maybe that is how it should happen. But our company is in your hands. We

will do it either way.

DR. McGUIRE: Does the committee have any questions at this point?

Dr. Bergfeld.

DR. BERGFELD: I have a question. In my background is as a dermatologist and a dermatopathologist, not a chemist. I fail to see how the drug is eliminated if you are unable to measure it in the urine. And if you say it is by hydrolysis, your metabolites that are hydrolysized are not present in the urine even. So, how is it eliminated?

DR. COLBURN: Unfortunately, I cannot give you a definitive answer on that, but I can give you a little bit of information, and hopefully document what I would anticipate is happening. The hydrolysis products are formed, but my belief is that they are quickly converted downstream to other products that we were unable to measure. And we only account for 1 percent of the thalidomide in urine. So, it obviously is not a major route of excretion. We anticipate that it is hydrolysis, but to products that we were not able to measure.

DR. BERGFELD: Is there any problem with this drug being stored in fat?

DR. COLBURN: Stored in fat? There is no evidence of that.

DR. BERGFELD: You have not measured the fat?

DR. COLBURN: No. We have not done any distribution studies of that nature. However, the characteristics of the compound would suggest that it is not going to be taken up in lipid material.

DR. McGUIRE: Dr. Shannon?

DR. SHANNON: Yes, sir, I found your comment about the using of the liver microsomes to study metabolites was not affected with Celgene's formulation. I wonder if you would comment on that, because that is a rather common protocol to generate metabolites of thalidomide, established in several laboratories.

DR. COLBURN: There's literature data that shows essentially what we've concluded here -- that hydrolysis, in fact, does occur. It occurs more quickly in liver homogenates, for example. But our data, based on the three metabolites that we measured, as well as parent compound, indicate that it is not through the cytochrome P450 system.

DR. SHANNON: How did you control for hydrolysis in that experiment, in the liver microsomes?

DR. COLBURN: You can't.

DR. THOMAS: I wonder if I could just add a point there, Dr. Shannon, and that is that even in the paper which I think you are alluding to, which is the

Knoche and Blaschke paper, they were only able to identify very, very low levels of these metabolites. And I think that is actually borne out in our data.

DR. McGUIRE: I think that is all for the committee right now.

DR. THOMAS: Okay. Thanks again, Wayne.

I would now like actually to pass the microphone over to Leo Yoder, M.D., recently retired from over 30 years of handling ENL and leprosy patients on behalf of the U.S. Public Health Service.

DR. YODER: Good morning. I am Leo Yoder. I recently retired from the Public Health Service after 15 years of working almost exclusively with leprosy, or Hansen's disease. Prior to that, I spent a number of years in Africa and also as a consultant in some other countries. So, I am talking to you briefly from the perspective of a person who has done hands-on care of patients, leprosy patients, and particularly patients with ENL, and lived through some of these difficult illnesses and experiences with them.

I will give you just a brief overview of leprosy, the syndrome itself, and then focus especially on ENL and its treatment, and my own experience and impressions in the management of this problem.

Leprosy is an infectious disease primarily of

man caused by Mycobacterium leprae. It is an unusual organism. It has never been cultured in a laboratory as of this date. It has a special affinity for skin and nerves, which are the cooler parts of the body, primarily the peripheral nerves, involving the hands and feet, and some other organs, particularly the anterior part of the eye. Testicles are often involved, as well. Especially also the respiratory tract, the nose especially.

Just a word about the problem worldwide as it still exists today. The World Health Organization uses the figure of 1 million to 2 million cases under treatment, which is the way they define prevalence currently. There certainly are an additional other 2 million or 3 million, at least, who have significant deformities and disabilities from this disease, who require care.

In the United States, we estimate approximately 7,000 or so cases that have been diagnosed and treated for the disease. Not all of these are now currently under treatment or have active disease, but these are on registers.

However, probably the more important numbers to look at what's ahead for this disease is to look at the new case rates, or incidence rates. In the U.S., approximately 200 new cases occur per year, or are reported per year. This has been fairly consistent. It is down slightly, but

this is not very much different from what it has been for quite a number of years, excepting for the mid-1980s when there were more immigrants from Southeast Asia.

Worldwide, as somebody has already mentioned, the current figure is about 600,000 new cases per year. And the significance of that number that I would make is that that number is not changing or decreasing very much. There are some notable exceptions to that in a few countries, but, in general, the number is going down very slowly.

So, in spite of the fact that WHO is talking about elimination as a public health problem by the year 2000, they are not reflecting the real new cases numbers, which are staying almost constant or decreasing very slightly. So, this disease is going to be with us for many years to come.

Leprosy is a spectrum of disease. From the simplest type of disease, tuberculoid disease on one side of the spectrum, patients in that category have a fairly intact cell-mediated immune response to this bacteria. These patients actually have very few bacteria. They have possibly one or two skins lesions or a few nerves involved. But the pathology is in excess of the number of bacteria. There is primarily an immunologic process that takes place and causes the nerve, or other, damages.

On the other end of the spectrum is lepromatous disease. These patients have diffuse, generalized disease, especially of the skin and nerves. They have a lot of bacteria in the skin and nerves. They have involvement of other organs, as I have already mentioned. They have a specific cell-mediated immune defect to this organism, Mycobacterium leprae. It is very specific for this organism. They handle other infections quite normally.

The other item of note is that there are antibody levels in these patients. In lepromatous patients, there are fairly high antibody levels. They do not do anything apparently to kill or clear these bacteria, but they do have some significance as far as ENL is concerned, which we will mention again later.

I am not going to talk about chemotherapy. There is antibacterial therapy which is quite effective, although it may take a number of years, but chemotherapy is effective. And I want to focus primarily on this problem of reactions.

This does not occur in all patients. The figures that one sees is anywhere from 10 to 50 percent, depending on when and what time frame you were talking about. But a significant number of these number of these patients do have reactions. There are basically two types of reactions.

One occurs in the tuberculoid end of the spectrum. And I should also say, in that spectrum, from tuberculoid to lepromatous, obviously there are a lot of patients who fall in the middle somewhere -- a big proportion of them -- and those are, in our lingo, known as borderline patients. And so patients near the tuberculoid end of the spectrum get something called reversal reaction, which is a cell-mediated reaction, quite different from ENL, usually treated with prednisone. And I will say nothing more about that.

On the other end of the spectrum, the lepromatous patients with high antibody levels and borderline lepromatous, the near-lepromatous patients, get erythema nodosum leprosum. These are not treatment failures. In fact, they can occur before treatment even is initiated, although usually they occur after a period of treatment. They are not drug reactions or drug allergies. They are, in fact, an immunologic problem.

There is a lot we don't know about that syndrome as yet. However, it is generally accepted that it is an immune complex disorder, antigen/antibody complement. Immune complex is deposited in the tissues, sometimes found in the circulation, although not always. And this produces an acute inflammatory response in the tissue, in the skin, a vasculitis, panniculitis. There is neutrophil

infiltration in these lesions, and these patients also have usually a rather significant leukocytosis in the peripheral blood, as well.

In recent years, it has also been noted that tumor necrosis factor-alpha is elevated in these patients, which decreases as the syndrome subsides. The significance of that is certainly not entirely clear at this point.

Now, turning to what this looks like clinically, the obvious visible thing is the skin lesions classically are erythematous nodules which look like erythema nodosum on the lower extremities from other etiologies. But these nodules can occur anywhere on the body, including the face, trunk, limbs. They can vary from mild, a few nodules, to extensive nodules. They are usually painful. They are easily palpable in the skin. I will show you just a few photographs of those. In the more severe cases, they can ulcerate and eventually produce scars as they heal.

This disease, to some degree, waxes and wanes. Even untreated, it will eventually end, but may take years, and the patient will experience a lot of pain and illness before that occurs.

But it is not only a skin problem. These patients, excepting for the very mildest ones, are acutely ill, with fever. Neuritis is common, although not always

present. As I said, they have a leukocytosis. They may be anemic. Other organs may be involved. They may have an orchitis, iritis in the eye. Nephritis used to occur. It's not so common these days since we treat it much more effectively and earlier. Lymphadenitis can occur.

The other part of the story is that this may go on and on and recur over a long period of time. It is rare, especially for the type of ENL that we see in this country, for it to last for only a short period of time. It usually, more typically, lasts for at least several years.

The diagnosis generally is not difficult. It occurs typically in a patient who is already on chemotherapy, sometimes for a year or two, and they think everything is going well, and then they flare up with these new skin lesions that may be associated with painful and tender nerves. They maybe have edema of the hands and feet. And usually there is acute febrile illness, where they have generalized aching and pain and malaise, and they are just generally ill.

These are just a few photographs of typical lesions. These lesions are on the chest on a gentleman, which is the classic type of lesion. Now, they don't look terribly striking as you look at them on a photograph, but if you palpate them, they are actually deep infiltrations

and generally are tender.

This is another patient who had been treated for approximately a year, doing well, and then developed these lesions on his chest. The same patient has these very painful lesions, which potentially are ulcerating, on his face.

Another young lady who had the typical erythematous nodules in the upper portion of her body and extremities, but she also had associated lesions, like this, on her lower extremities, with ulcerations and blisters.

A patient with actually sterile pustules, painful lesions on the arms.

Finally, this is a young lady who I lived through. I worked with her for a number of years, managing this reaction. You may not appreciate it in the photograph, but she is quite cushingoid from long-term use of steroids. In spite of that, with our best efforts, she still had ulceration of her face. And that is typical of some of these very difficult young ladies that we see occasionally, where this disease process continues for several years.

The treatment options for this problem, other than for the very mildest ones, really are very few. For the mildest ones, which we rarely see in this country -- I

used to see these in Africa occasionally -- you could simply treat them with analgesics. But much more commonly in this country, they are more severe than that. And we really only have, for the acute situation, only two options. The standard of treatment in our field now is thalidomide as the drug of first choice if it is in a situation where it is available and not contraindicated, as we will mention, especially women of childbearing age.

Prednisone and clofazimine are the other alternatives, and I will briefly address those.

First of all, clofazimine is used and can be used in some cases, but it's slow acting. It has a number of disadvantages. It is not useful in the acute stage because it takes a month to 6 weeks at large doses -- 200 to 300 milligrams a day -- to get an effective therapeutic effect. At that point, it does have a steroid- or thalidomide-sparing effect, and it is useful in patients who have severe problems.

But there are other disadvantages to it. One is skin pigmentation, which occurs in virtually 100 percent of cases, which is unacceptable in many patients, particularly in light-skinned persons, and especially in young women.

There are also gastrointestinal symptoms in patients who take large doses. And most patients will not

tolerate 300 milligrams a day for more than 6 weeks or so. The dosage then has to be reduced. And occasionally I have seen patients who have had severe gastrointestinal symptoms, and even bowel obstructions have occasionally been reported at large doses.

This is a photograph of a person who has taken clofazimine for a considerable period of time, and you can see the skin pigmentation over his face and arms. Typically, this pigmentation occurs where the bacterial load is large and inflammation is taking place.

Corticosteroids, or commonly what we use is prednisone orally, is effective. There is no question about the efficacy if you use large enough doses. The doses do need to be large. Many times in the U.S. we generally will have to start with 60 to 80 milligrams a day. We have often used even larger doses than that. And these need to be given for long periods of time. As I mentioned, this continues for extended periods -- often years -- and so you will require these large doses for a considerable period of time.

If you attempt to withdraw the steroids, the reaction will tend to occur. And, for the most part, short courses of prednisone do not work. If you withdraw them, they will simply recur again. I am talking about 2 weeks or so, and stop them. It is not an efficacious or a good

way to manage these patients.

Consequently, many of these patients who do not have access to thalidomide, or it is contraindicated, develop serious side effects from the prednisone. These are well known to you physicians who treat patients with cortical steroids -- osteoporosis, collapsed vertebrae, weight gain, diabetes, cataracts. We've seen all of those in some of these patients who had to, for various reasons, take steroids for long periods of time.

And one of the benefits of thalidomide is the avoidance of these significant side effects and, occasionally, even life-threatening situations that can develop from patients who take steroids for long periods of time.

Thalidomide is effective in the acute state, often as monotherapy, or in combination with steroids and clofazimine, as I mentioned. But the other important use of it is in maintenance therapy. Once the acute stage is controlled, to maintain these people on thalidomide for extended periods of time will prevent the recurrence of these episodes. So that further steroids or only very low doses of steroids are required for the period of time that it takes for this patient to clear the bacterial load.

The potential for these reactions to occur is as long as the bacterial load or the antigens of the

bacteria remain in the body. And the antigen, incidentally, in leprosy clear very slowly. It takes years to clear these bacteria out. Even though the antibacterial therapy is effective, the dead bacteria remain for years -- 5, 6, 7 years, sometimes longer -- before they actually are completely cleared.

As was mentioned already, thalidomide has been the standard of therapy, recommended therapy, for ENL for many years, including the World Health Organization. There has been a large experience with it in many parts of the world.

At Carville, there has been an IND for the use of this drug since 1975, which will be mentioned and will be discussed in some further detail later by another speaker.

This IND has made it possible to use thalidomide in leprosy patients, but it is restrictive, in that every physician who desires to use the drug has to obtain approval from his own institutional review board, wherever he is located. He has to go through a considerable process to get that done and then to obtain it. Under this protocol, it can be given to males and post-menopausal females as an outpatient.

For childbearing age females, the requirement is that they must either be surgically sterilized, which

has been done on some occasions because of the chronicity and the severity of the illness, or they would have to be hospitalized at Carville, in the hospital for the duration of the time that they take the thalidomide -- which, during that time, they would be on contraception and weekly pregnancy tests.

Finally, just a word from my own experience and the experience with that IND for the last 20 years or so as far as adverse events are concerned. In our experience, we have not seen any congenital deformities that have ever been reported to us under these conditions.

Sedation is very common. However, this is generally not a significant problem when it's given in the hospital, of course, or, in general, as outpatients, it is given as an evening dose, and most people develop a tolerance to this and manage this quite well.

Peripheral neuropathy has always been a concern. We have known about this. Even before this IND was initiated, it was reported. In addition, we are dealing with a neurologic disease, so people who treat leprosy patients are sensitized to the fact that we have a neurologic problem.

Patients who develop reactions and are treated appropriately with thalidomide or prednisone generally do not develop further deterioration in their neurologic

status. These patients are all evaluated at baseline, with various methods and, on occasion, not all, but some, with nerve conduction studies. There are also other ways that we do sensory testing. And so these patients do get looked at for neurologic problems.

Our experience has been that we rarely, if ever, see any significant deterioration in the neurologic status after we start treatment. Now, we are aware that there is the possibility that we could be missing occasional thalidomide neuropathy which presents as a tingling and a paresthesia primarily. But the experience is that we do not see any significant deterioration in neurologic status with these patients on treatment.

We have seen it on occasion, and we have, on occasion, seen situations where the time frame of the neurologic symptoms suggested that it could possibly be thalidomide, and it would be discontinued in that situation. But overall, our impression is, as in many others, that thalidomide neuropathy either is very mild in leprosy patients or occurs very rarely.

The other items on there -- peripheral edema, constipation, leukopenia, rash -- are occasionally seen or reported, but they are almost always of very mild nature and manageable and almost never require the discontinuation of the drug.

So, in conclusion, I would say that, in our experience this has been a very useful and efficacious drug in management of these patients with a very difficult chronic problem. And I think that we have been able to show that, under properly controlled and monitored situations, it can be used safely.

DR. McGUIRE: Thank you, Dr. Yoder.

Are there questions from the committee? Yes.

DR. KILPATRICK: Dr. Yoder, I missed something in the write-up, perhaps. As a statistician, I'd like to know, in your own experience, what percent of ENL patients are women of childbearing age, let's say, in the United States and/or in Africa?

DR. YODER: Well, the proportion of males to females with leprosy overall is something in the order 60/40. You know, there are more males than females.

As far as proportion of those that get ENL, I am not aware of any sex differences there. And the proportion that get ENL ranges widely. In the literature, you see reports as high as 50 percent. I don't think, certainly, it's that high in the United States. But I am not aware of any specific sex differences in the ratio.

DR. McGUIRE: Dr. Hashimoto.

DR. HASHIMOTO: Apparently you did not have any pregnancies in your institution, so the teratogenicity is

zero.

DR. YODER: Yes.

DR. HASHIMOTO: How many reproductive-age patients have you treated since 1975? And you mentioned sterilization, but that is not very practical outside of an institution. What would you recommend? What would you be comfortable with, other than the method of sterilization? Is the contraceptive pill enough, or what do you think?

DR. YODER: Well. I think if you were going to use it as an outpatient, it would be important that you would use at least two methods of contraception. Certainly an ideal would be if you would use some method that does not apply to compliance. But I think it would require a very stringent program, and I think we will hear more about that, later today, what Celgene's proposal is to do that. But I think it would require a very stringent one, with at least two methods of contraception, regular pregnancy testing.

At Carville, we did weekly pregnancy testing -- that may have been a little excessive -- along with very stringent requirements for mandatory education and consent forms and so on. So, I think it would take a very stringent program.

DR. McGUIRE: Dr. Orkin.

DR. ORKIN: Is the pigmentation with

clofazimine persistent, continuous, permanent?

DR. YODER: No, it will fade. It takes 6 to 12 months, or sometimes even longer, for it to go away. But generally it does go away after you stop the drug.

DR. McGUIRE: Dr. Crawford.

DR. CRAWFORD: Do you warn the patients that they might develop neuropathy from thalidomide?

DR. YODER: Yes. It is included in the consent form. All patients sign a consent form, and the neuropathy is in there, and of course, it is always discussed with the patient. Of course, we are dealing with leprosy, which is a neurologic disease, so we are discussing neuropathy which may occur from leprosy as well.

DR. CRAWFORD: Have you any clinical data on the state of the peripheral nervous system before thalidomide is started? Because, in my experience, patients with ENL may not have involvement of the peripheral nervous system because it's lepromatous leprosy, which is treated. The viable count or the morphological index falls to normal in many of these patients. Clinically, anyway, they have a normal examination of the peripheral nervous system. Have you any data of that before you start thalidomide?

DR. YODER: All our patients do have a neurologic evaluation before they are started on treatment.

Is that what you were asking?

DR. CRAWFORD: Yes.

DR. YODER: Yes.

DR. McGUIRE: Dr. Shannon?

DR. SHANNON: Yes, Leo, I ask this question in the context of we are here to meet, and maybe one of the things that is thought that thalidomide does is suppress tumor necrosis factor-alpha, and clearly it does in the conditions. I'm asking this question to draw from your experience as a clinician, particularly in Africa, and to address the comment on reversal reactions, where immunologically there is a lot of indication that TNF-alpha message and protein is in reversal reaction lesions, yet I hear anecdotally from a lot of clinicians that thalidomide does not work in reversal reactions. So I have to ask you your opinion, your observation, if that is correct.

And then, the other question is, have you had any experience with pentoxifylline, which is classified as an anti-TNF-alpha drug in the treatment of ENL?

DR. YODER: The first question, it is my impression that thalidomide does not work in reversal reaction. And we occasionally have patients in the borderline group, where it is clinically sometimes difficult to be sure of whether they are having ENL reversal reaction and, on occasion, we find no response

from thalidomide. So, it is my opinion that thalidomide does not work in reversal reaction.

The other question, regarding Trental, is that we have used it in a few cases -- simply on patients at Carville -- not a formal clinical trial. Our impression was it is not dramatic. It may be a mild benefit in several cases that we have used it on, but I am not impressed that it is -- it certainly is not a miracle drug in this disorder.

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

DR. SIMMONS-O'BRIEN: Dr. Yoder, I'd like to know what actually comprised your neurologic evaluation and how often was it repeated. What were the intervals of evaluation for all of the patients?

DR. YODER: Well, you will see some data later. This data is collected from a number of different centers around the country. And actually the report forms that came in -- there were a large number of centers that report here. And so I am sure there will be considerable variation as to the type of evaluation.

If I can respond to specifically what we do at Carville. At Carville, of course, the physician does a neurologic examination. Then all of our patients are seen in the occupational therapy department, who do a sensory testing and motor testing of the upper extremities, using

monofilaments, graded monofilaments. Similar evaluations are done in the physical therapy department for the lower extremities.

Nerve conduction studies are not done in all cases. If it appears that they will be useful or if we have difficult problems to sort out, they will be done also.

The frequency with which they will be done will vary. If we had somebody in the hospital who had evidence of a neuritis and possibly changing neurologic status, they could be done as often as every 1 to 2 weeks. There is not a standard protocol.

Beyond that, if there is no change or evidence of neuritis, then clinically they would probably generally be done. The first few years, we would do them as often as twice a year on their visits. Standard procedure was that if they come for a routine follow-up, they would have one done at least once a year. So, it would vary considerably on the actual clinical situation.

DR. McGUIRE: Dr. Duvic has the next question.

DR. CRAWFORD: Could I just add a word about your figures? Can I bring you up to date?

The WHO, at the moment, has 900,000 patients on treatment. According to the mortality and morbidity, July the 18th, there were 53 new cases of leprosy reported. And

last year, 112, which are considerably lower. I think this is important, in view of Celgene's use of the drug -- that the numbers may be quite small. And of course, only a proportion of those will have ENL.

DR. YODER: I missed your last numbers.

DR. CRAWFORD: Fifty-three.

DR. YODER: Of what?

DR. CRAWFORD: New cases of leprosy. That is the mortality and morbidity report for July the 18th. That is the latest figure we have in the U.K. And last year, 112 new cases.

Now, those are all cases of leprosy. And of course, only a proportion of those will be lepromatous leprosy, and only a proportion of those will have ENL, depending on -- 5 to 20 percent.

DR. YODER: Are you giving those numbers for the United States?

DR. CRAWFORD: Yes.

DR. YODER: Well, I would disagree with those numbers. I'm giving you numbers from our registry at Carville.

DR. McGUIRE: I think these are U.K. numbers you are offering.

DR. CRAWFORD: No, no. These are the USA mortality and morbidity published by the CDC.

DR. McGUIRE: Okay.

Yes.

DR. DUVIC: Dr. Yoder, from your experience, what percentage of patients who get ENL would you use thalidomide in? And of those, what percent would benefit from it, having improvement that was clinically significant?

DR. YODER: I would use it in virtually all of them if it was available, or if it was not a female of childbearing age. Those you might, because obviously most of them would not want to be sterilized or be hospitalized at Carville. You would use something else.

But if it was a male or a surgically sterilized female already, or post-menopausal female, thalidomide would be the drug of choice in virtually all of them.

DR. DUVIC: And of those, how many would it help? What percentage?

DR. YODER: The vast majority. I would say better than 90 percent.

DR. DUVIC: Okay.

Why is it assumed that women are so stupid that they can't use birth control for a drug that causes this kind of birth defects? Why do you assume that someone has to be sterilized surgically? Give us a break here.

(Applause.)

DR. YODER: This is not my assumption. But let me tell you why the situation exists. This is the way the IND was set up in 1975. And actually, the original protocol did not exclude women of childbearing age.

However, that protocol had to be approved by the Tulane University Institutional Review Board, which is standard for any kind of investigation program. And they came back and told Dr. Hastings in 1975 that they felt that the liability for Dr. Hastings and the Public Health Service, et cetera, were too great and that they should prohibit women of childbearing age from receiving the drug. And, therefore, they complied with that. And that is the way it was submitted to the FDA. And that is the historical reason for it.

DR. McGUIRE: Dr. Moore.

DR. MOORE: Yes, I have one question, and a follow-up actually, to Dr. Crawford's question.

In your experience, Dr. Yoder, how successful have U.S. clinicians been in getting the thalidomide they need to treat their patients with ENL?

And my follow-up to Dr. Crawford's question is, you said the figures that you gave us for incidence and prevalence came from Carville, but can you tell us exactly what the sources are from those data? Because, again, they are higher than estimates we have received from our

infectious disease --

DR. YODER: You are from?

DR. MOORE: The CDC.

DR. YODER: Okay. There are several ways that we get our data. And this has a fairly long history that the figures from CDC are fewer than ours. I am not sure how CDC gets their figures, but ours, some come directly from physicians. We get a lot of biopsies sent to us from all over the country. In addition, we have eight contract centers around the country. If we get a biopsy at Carville that's positive, our medical records people will contact that physician and get the appropriate information. So, there are various sources that we collect information from that probably does not get to CDC.

I know there have been discussions about exchanging data, and apparently that has not taken place.

You had another question I think.

DR. MOORE: The first question was, in your experience, how successful have U.S. physicians been in getting the thalidomide they need to treat their patients who have ENL?

DR. YODER: You are questioning the availability of thalidomide?

DR. MOORE: Have there been problems getting the thalidomide?

DR. YODER: There was at one time, yes. A number of years ago, we used to get it from Germany, Chemie Gruenenthal. They eventually refused to sell it to us anymore for various reasons. So, at one time, there was no source. And there was an agency that compounded this for us, and we actually put it in capsules at Carville, and partly manufactured it ourselves. Then we eventually went to foreign sources, and there was some problem with the quality of some of those.

In more recent years, we had been able to get somewhat better-quality thalidomide from Brazil, actually. So, in recent years, we have not had a shortage of product. But there have been problems.

DR. McGUIRE: Dr. Yoder, we are going to let you finish, but I did want to ask one brief question. What is the total number of ENL in the United States per year, including repeat? These are not necessarily new ENL, but you could include the repeat.

DR. YODER: Yes, the annual report usually has been in the range of 200 to 225, and maybe a little more than that. That is the approximate number of cases that we report on that IND annually that goes to the FDA.

DR. McGUIRE: This is ENL, not new cases of leprosy.

DR. YODER: This is patients that are on

thalidomide for ENL, yes. That's right. That is exactly right.

DR. McGUIRE: Thank you.

Dr. Thomas, do you want to take over again?

DR. THOMAS: Thank you very much, Dr. Yoder.

I'd just like to alert everybody in the room that as well as having Dr. Yoder here as a learned expert, we also have available in the room actually Dr. Tom Rea and Dr. Bob Gelber, who also have extremely extensive experience in actually dealing with this indication. And if, at a later date, or as a result of other discussions, you think it would be useful to get their perspective, then please just let me know.

I'd now like to pass you over Dr. Jerry Zeldis of the Celgene Corporation. He will actually present information on the safety and efficacy of the drug as it pertains to that information which is in the NDA package.

DR. ZELDIS: Thanks, Steve.

First of all, good morning. My name is Jerry Zeldis, and I'm Vice President for Medical Affairs at Celgene. I am very privileged today to be able to present to you both the efficacy and safety data that was presented in our application.

The first aspect of our application I would like to discuss is efficacy. And it is quite remarkable

that since this drug was discovered in Israel around 1965 to be effective or potentially effective for treating ENL, there has been extensive literature on the use of this drug for treating this condition, and there has not been a single article that ever questions the efficacy of using thalidomide for treating ENL.

I want to harken back to some words that Mary Pendergast said in the beginning of this session today. This is orphan indication. And by hearing Dr. Yoder talk about the numbers of cases, and Dr. Crawford backing him up with even lower numbers, this is an orphan indication. You have to look at both the historical published literature and the experts who are actually in the field, arm deep in the syndrome, and trust their judgment, besides looking at randomized, controlled clinical trials.

And I hope the committee keeps an open mind as I present to you this, admittedly, by 1990 standard, flawed data set. But it isn't as flawed as perhaps I imagine or perhaps that others would purport.

Let me get to the first slide.

There are basically four elements to our application which I'll discuss today. Basically, the literature, which composes experiences of over 1,800 patients. In addition, there was a survey conducted among Hansen's disease treatment centers, which provides

information -- at least a global overview -- of how over 4,700 patients have fared with the drug.

This literature, as Mary Pendergast mentioned earlier, there were over 50 -- actually, I think it was the pediatrician who mentioned it earlier -- there were over 50 brand names for the drug. This represented various lots from many different companies. Even within the same companies, there was lot-to-lot variation. With the exception of a few manufacturers, most of this drug was not made by the standards that we would consider good manufacturing practices and controls. Despite that, the literature is uniform in praising the effectiveness of this drug.

In addition, Celgene was able to obtain an electronic data set which contained 19 years of data from Carville's experience. The case report forms from which this data set was derived was not completely audited, but we did audit 2 years' worth of data and found very good congruence between what was in the case report forms and what made up the data set.

We also went back to Carville and audited the medical records of patients who underwent a study at Carville by Dr. Hastings, which was a double-blind, placebo-controlled trial, although not done under the rigorous good clinical practices protocols that is required

by 1990's standards, which also demonstrated that the drug is effective in treating ENL.

And, finally -- and actually, to begin with -- but, finally, I am going to talk about a Celgene study which is currently being performed in the Philippines. At this juncture, 21 subjects have entered the study. It is a double-blind, dose-comparison trial. And I will present a blinded interim analysis of the results on this study.

If you look at these four lines of evidence, the only evidence which is being done, which was collected under good clinical practices, under the types of, I'd say, clean data sets and assurances that the FDA normally requires for a larger drug application for a more prevalent indication is this ongoing study. But, despite that, I think you will see that the weight of evidence will show that this drug is effective and also safe for treating ENL.

I would like to first give you my overall impression of this data set, and then I'll go into specifics.

Despite how response was defined in these various studies and data sets, we have found that greater than 90 percent of patients will respond, if they have moderate to severe ENL, to thalidomide treatment.

Furthermore, their response rate is similar regardless of the type of anti-lepromatous regime used --

whether they are given the intermittent WHO regimen or the more continuous regimen which is being used in the United States.

Furthermore, as Dr. Yoder said earlier, the drug is steroid-sparing. It prevents steroid rebound. It has been used as an effective single agent even in patients who were deemed to be steroid dependent -- meaning that you could not get them off steroids without getting a severe steroid rebound -- and is effective both in the acute treatment of ENL as well as in maintaining remissions.

Furthermore, in some individuals, a complete response -- that is, the absence of not only the skin lesions or new skin lesions being formed and healing of the old ones, but also the systemic problems as well, can disappear within 1 to 2 weeks of initiating therapy. In others, it takes longer. However, in virtually every patient who will respond to the drug, a response becomes evident in as short a time as 48 hours after initiating therapy.

The response rate does not appear to be affected by the age, the sex, and the race. And this is supported especially in both the literature and the Carville experience.

While the painful skin lesions and the fever respond first, the other symptoms that make up the syndrome

will respond with time. And, furthermore, it is the observation in both the literature and Carville that steroid-dependent subjects resolve more slowly.

I would like to now turn our attention to the Celgene study, E-003/P, which is currently being performed in the Philippines.

The rationale for the study was to perform a study that showed that Celgene's formulation was effective in treating ENL. While Celgene wanted to do a placebo-controlled clinical trial, it simply cannot be done in the late 1990s, period. We talked to our advisors. We went to IRBs, ethics committees and other similar institutions around the world, and we could not find an expert. We actually went also to the leprosy foundations. We could not find anybody who has experience with this disease who felt that it was conscionable or ethical to do such a study.

So, therefore, we were left with the fact that we need to do either a drug comparison trial or a dose comparison trial. When we looked at the alternatives for therapy, it was felt by our experts that there really wasn't a good drug to compare it to. These had been done in the older literature, and that it was not felt -- the trouble with steroids was such that it was not a good dose comparison trial to try to do. So, after an extensive

dialogue with the FDA, it was agreed that we would do a dose comparison trial.

Why did we pick the Philippines to do the trial? Well, in the United States, as you have heard, there are just not enough patients, and most patients who are diagnosed with ENL go on to thalidomide as fast as they can jump through the regulatory hoops.

The Philippines, however, presents a different situation. There is enough of a population of people who have leprosy and who are thalidomide naive or are not being treated with thalidomide that we could actually perform a trial in a reasonable period of time.

The purpose of the study was to compare two doses, either 100 milligrams a day or 300 milligrams a day, a 7-day treatment, for treating mild to severe ENL. After, if the patients responded to the drug, we then looked at what happened if you tapered the patients off the drug, and the time to relapse after successful treatment.

Design of the trial was straightforward. Patients were, in a double-blind manner, randomized to receive either 100 milligrams per day or 300 milligrams a day of thalidomide. Patients to be entered had to have moderate to severe ENL confirmed histologically. Furthermore, patients who were deemed to have mild disease or life-threatening disease were excluded from this

protocol.

Even though patient status was judged on a daily basis, at 7 days, the subjects were classified as either a complete responder, a partial responder, or a treatment failure. Those patients who were partial or complete responders then entered into a tapering phase. And at the end of the taper, the extent of their disease was then reassessed.

The rating scale was based on two aspects: the presence of fever and the presence of skin lesions. A complete responder had to have, at the end of the 7 days, the absence of fever and no acute or active skin lesions occurring. If they had one or the other, but not both, they were considered a partial responder. If they had fever and they had active lesions, they were considered a treatment failure.

There was a clause built into the protocol that if after 72 hours the patient received an analgesic, by definition, they were a treatment failure, period. Furthermore, if they received steroids at any time, they also automatically were deemed a treatment failure.

I would like to get back to this point in about two minutes.

What we submitted in our initial NDA package in December was a blinded database consisting of nine

completed subjects. Now, every subject either received 100 milligrams or 300 milligrams of thalidomide.

I just want to make one point which Dr. Yoder mentioned, but I want to emphasize this. While the lesions of ENL do wax and wane, it is extraordinary and probably beyond anyone's clinical experience to see a patient who has many lesions on their body to have none 7 days later. When ENL burns out, it is a slow burn. It is a slow resolution, which often takes months. In fact, I doubt you can find a diagnosed patient with ENL today who is not receiving therapy. You just don't find the natural history of this disease which is not treated anymore.

Anyway, what we have done in the last few weeks is go back to the Philippines and collect another blinded data set. We have efficacy data on 16, and now it is up to 17, patients. We added a patient last night, although the data set, I believe, was delivered to the FDA last week. The reason why we have more safety data than efficacy data is that 1 patient was admitted into the study who had neuritis due to ENL, but did not have skin lesions and, therefore, we cannot assess efficacy in that patient. You can't analyze that patient.

The target is to bring 30 patients into this study, and then we will un-blind the study.

At baseline, all subjects had fever and all

subjects, except for the one patient who we exclude from our efficacy analysis, had greater than 40 skin lesions on their body. Some people had more than 80.

Systemic complaints included fatigue, chills, anorexia, mild arthralgias, neuritis, painful lesions, and nasal congestion.

This is the results which we have determined. And they are similar to what was in your package, although now we have more patients.

I just want to make one point about this. These patients were classified based on the treating physicians in the Philippines. Here is the data on the 16 patients.

At the end of 7 days, 9 were deemed to be complete responders; 5 were partial responders; and there were 2 treatment failures. Now, we do not know the doses that they received.

The acutely inflamed nodules healed in everybody between 2 to 5 days. The patients who had ulcerations on their skin, the ulcers healed within 2 days; the pustules resolved within 5 days. Both treatment failures were then placed on open-label thalidomide at 300 milligrams per day, and both responded to therapy.

Now, I have been told -- I was told this last night, I think around 12:30 in the evening, when we looked

at the data set one last time -- that both these patients, after they responded, went off thalidomide. They relapsed, and they were then re-randomized and put back into the study. And so, when the FDA is looking at the data set, they will notice that we actually sent them more patient information, but we identified these as repeat patients in this study. It doesn't change the conclusion.

But, furthermore, when you look at shift tables at 7 days, what you found was that the following ENL symptoms improved in these patients: Anorexia disappeared, arthralgias, chills, shortness of breath, fever, malaise, nerve enlargement and tenderness, neuritis, orchitis pain, rhinitis, and vasodilatation.

In the patients who were treatment failures, these symptoms worsened, but it was only in these patients: One person had epistaxis, and epistaxis is a complication of lepromatous leprosy and ENL -- chills, edema, fever, malaise, neuritis, and pain.

Now, what happened after what happened after tapering -- and let me walk you through this semi-complicated slide. These are the 9 patients who initially were deemed as complete responders, and at the end of their taper, only a few remained complete responders. The rest either became partial responders or treatment failures. These are the 5 patients who, at the

end of 7 days, were diagnosed as being partial responders. It turns out, at the end of the taper, 4 of the 5 were now deemed complete responders and the fifth was now a treatment failure. That is a "TF," not a "TR."

Our conclusions from the study are that thalidomide is capable of inducing a complete response and partial response in patients with moderate to severe ENL. Furthermore, withdrawal of thalidomide may result in disease recrudescence.

Now, I would like to just briefly bring up the overhead.

As I said, around 12:30 last night, we were rummaging through the database and looking at concomitant medications. And what we discovered was that there was a protocol violation. 5 subjects continued to take acetaminophen, or paracetamol -- the same drug -- for 4 days. And, therefore, by definition, these 5 automatically had to be reclassified as treatment failures. It does not change the overall conclusions of this study.

When we reclassified these patients, we still find that 10 of 17 people responded to therapy.

What happened to these 5 people who were, quote, treatment failures, because they took acetaminophen 4 days into the protocol. Now, at this point, they were off paracetamol or acetaminophen. And as you can see, it

breaks down now. Again, this person here, who is a treatment failure, was not deemed a treatment failure by the physicians, based on skin lesions and the absence of fever. He now is definitely -- we have one partial responder.

Okay. I'd like to now go on to the Carville experience.

As Dr. Yoder explained, since 1975, the Public Health Service has maintained an IND with the FDA to allow the treatment of people with ENL with thalidomide. And in many respects, Carville became the conduit for thalidomide therapy in the United States, not only actually for leprosy but for other conditions as well.

Now, I am going to tell you what was in the protocol, and I will also tell you what happened -- at least my interpretation of this, and I am going to rely also heavily on Dr. Yoder to help clarify any interpretations or questions that I may have.

Patients were admitted into this IND if they had biopsy-confirmed severe borderline leprosy or lepromatous leprosy. They were allowed to take various anti-leprosy medications while on therapy with thalidomide, and they were evaluated every 2 months.

On an annual basis, the treating physicians would complete a case report form and send it to Carville.

This included demographic data, dosing data; the physicians were asked to write down any adverse event or side effect that they believed was drug-related. So this is different. In a normal GCP, or good clinical practices, you write down any adverse event that occurred, not whether it is drug-related or not. And they were asked to give a global assessment of how the patients were doing.

I will just say parenthetically, again -- and I would like to reiterate what Dr. Yoder said earlier -- since the early 1960's, everyone using thalidomide has been aware of the peripheral neuropathy caused by thalidomide. And this was in the informed consent. And every patient who received the drug and every physician who used it was aware of this and was looking for this.

Subjects were rated on a yearly basis as being good, in good control -- and this is a global assessment. So, if they had partial control, they were fair; if they had no response or they were treatment failures, it was poor, unknown, or lost to follow-up.

By protocol, subjects were supposed to take 100 milligrams four times a day of thalidomide. The reality is that, as more experience with the drug was accrued, most physicians gave the drug at bedtime and at lower doses, but it also depended on the type of drug that they were receiving. Certain batches of drugs from certain

manufacturers appeared to be so ineffective that subjects were told to chew the tablets to try to increase the availability so they could respond. There was tremendous lot-to-lot variation.

If they got their ENL under control, a taper would begin. And the actual dosage used really depended on the judgment of the clinician. If the clinician saw what they considered a very severe case, they would tend to start at a higher dose. If it was moderate, they would get a lower dose.

Also, the response. If initially the patient was started on a lower dose and they did not respond as well, they would go to a higher dose.

Also, on drug availability, there were a few crises, where it looked as if the U.S. was going to run out of drug, and there was some rationing going on.

Every 6 months, physicians were encouraged to try to wean patients off the drug. If they had an ENL relapse, the patients could be re-treated again with thalidomide, and the maintenance dose suggested was anywhere from 100 milligrams every other day to 50 milligrams twice a day.

Basically, each year Carville collected between 227 to 341 case report forms, for a total of 4,767 case report forms collected between 1978 and 1994. In the

beginning of the program, you had the most case report forms collected, because you had the largest pool of people who were getting thalidomide for the first time.

This translated into 33 to 234 new patients initiated each year, for a total in this experience, over 17 years, of 1,367 patients who received the drug.

The age range was mostly between 18 to 64, but there still was a significant number of people above and below that range. About 20 percent of the patients were women, although as Dr. Yoder explained, the women who we have records on were either surgically sterilized or hospitalized in Carville for the duration of their thalidomide treatment.

The ethnic makeup of this group was consistent with the ethnic makeup of leprosy that we see in the United States: mostly Hispanic, Asian and white.

85 percent of the patients had lepromatous leprosy. About 15 had borderline leprosy. And the average patient had the Hansen's disease for at least 5 years.

The average mean dose during the initial course of therapy was about 132 milligrams per day, although there was a wide variation. And, again, you have to understand that many different manufacturers' drugs were used, and there was tremendous lot-to-lot variation even within the same manufacturer.

The average duration of treatment was 3.3 years. Even though the dose went down with subsequent years of therapy, at year 3 it was virtually the same as in year 1. The longest treatment duration of any patients in this 17-year database was 14 years.

How did these patients do?

At the end of the first year, when we looked at the case report forms, 79 percent of the people were complete responders; 17 were partial responders. That means 96 percent of the people responded. The rest either were treatment failures, very few lost to follow-up, or it was not rated. It's not known.

When we looked at the response to continued treatment, we found there were three things that were readily apparent. Complete responders tended to remain in complete response. Greater than 90 percent of people who, at the end of year 1, were rated as complete responders remained in complete response over the next 10 years. Partial responders also improved with prolonged therapy. Year by year, a higher percentage of the partial responders became complete responders.

This is important, because patients on steroids respond more slowly, and it may take them over a year to go into a complete response.

Furthermore, some treatment failures -- about

half -- with continued therapy, became responders.

When we did subset analyses, we found that the initial response was unrelated to the dose of the drug used, to the age, the gender, the race, and the type of concomitant medication they were being given. And I can tell you that the drug was being given as monotherapy, as co-therapy, and as adjunctive therapy in these patients.

So, our conclusion from this large experience is that thalidomide is effective for treating ENL as monotherapy, co-therapy, and adjunctive therapy, and that continued use of the drug is associated with increased response rates.

The next leg of data on this table -- it is a four-legged table -- is the Hastings study, performed in the late 1960s and published in 1970.

Now, what Celgene did was go back to Carville, find the medical records, and actually abstract the medical records as if this was a brand-new study, and put together a data set, which we then analyzed.

Because this was not a GCP-conducted study by the standards in the 1990s, it is not surprising that there were patients in that we identified who were not in the final publication by Dr. Hastings. When there was a doubt about what happened, we excluded the patient from our database. We feel very confident about the way that we

abstracted the data.

Basically, this was a double-blind, placebo-controlled trial. And to enter the study, patients were taken off all their therapy for ENL. Many of these patients were on steroids. And after 4 days, if the patients developed new skin lesions and fever, they were allowed to enter the study. Many of these patients had steroid rebound and therefore had a severe response.

They were then, in a double-blind manner, randomized either to receive 100 milligrams a day of thalidomide four times a day or placebo. A response was defined as, at the end of 4 days' treatment, the patients had to have the absence of fever and no more skin lesions. A failure was defined as having either both new lesions and fever or one or the other. So, this is a very stringent study. You have 4 days to respond or you're out.

At the end of 4 days, patients were crossed over to the other regimen or entered open label.

Celgene identified 25 patients who were treated during this period when Dr. Hastings ran the study, who were treated in a manner consistent with being in the Hastings study. Again, this is not as if we went and pulled the case report forms.

About half of them were on dapsone. 88 percent of them were male. The ethnic mix is consistent with what

Carville sees. And the results are absolutely straightforward: The drug, thalidomide, was superior to placebo in healing acute ENL, based on loss of fever and loss of new skin lesions and at the p less than 0.005 level. 10 of 12 thalidomide-treated subjects responded as opposed to only 3 of 13.

Now, if you go back to the original Hastings paper, he states that none of his placebos actually responded. Because we were being conservative, we believe that there were 3 who actually did, based on his criteria.

Equally important, 8 placebo-treated patients who failed therapy were subsequently treated with thalidomide, and all of them, 100 percent, responded within 4 to 11 days. Furthermore, when patients had relapses off thalidomide and they were placed on thalidomide, the majority of these episodes did respond to repeat therapy.

Our conclusion is that thalidomide is more effective than placebo for alleviating fever and preventing new lesion formation in ENL.

The last leg on this table of efficacy is the published literature. And it is quite extensive and quite varied, and it also involves different lots from the same manufacturer, with different availability, as well as many different manufacturers. But the results are absolutely consistent throughout the literature: The drug works.

There were five controlled trials published in addition to Dr. Hastings' -- 168 treated patients. The response rate was greater than 90 percent. And these responses included studies which looked at responses for skin lesion healing, absence of fever, resolution of neuritis, orchitis, arthralgias, headaches, anorexia, uveitis, lymphadenitis, and fatigue. In one study, which was a double-blind comparison trial between aspirin and thalidomide, thalidomide was superior.

Thalidomide also was deemed to be steroid-sparing.

When you look at the open label trials -- there were three of them, involving 313 patients -- all three are unanimous: Improvement occurred within days of starting the drug.

Furthermore, thalidomide was superior to standard therapy, which at that time did not include thalidomide.

Thalidomide also was superior to chloramphenicol.

And when you add clofazimine to thalidomide, the results were actually superior than when you used thalidomide by itself.

And 27 studies, involving 1,378 patients, were open-label, non-comparator studies. Again, what we found

by reading this literature was progressive clinical improvement in 48 to 72 hours, including the loss of fever and painful skin lesions. All studies found greater than 90 percent response. This is very repetitious. I'm sorry, but that is the literature.

Thalidomide allowed continued anti-leprosy treatment. It is steroid-sparing, and if you rebound after you are off the drug, or you react after the drug, you can control it by going back onto the drug.

The survey which I alluded to earlier of Hansen's disease research centers around the world showed that 95 percent of 4,769 patients who were evaluated by their doctors had a satisfactory or excellent response to being treated with thalidomide. So, the world out there feels that this drug works. The clinicians in the trenches feel this drug works.

As far as case reports, there are 20. In 19 of these cases, the patients responded. 1 patient was discontinued from the drug shortly after beginning the drug due to an ulnar nerve abscess.

So, in conclusion -- at least on this part of my talk -- I think I have now presented to you four lines of evidence that this drug is efficacious in treating ENL, the first being our own study, showing that our formulation is effective in treating ENL, as judged by the loss of skin

lesions and fever, and that stopping the drug leads to disease recrudescence.

Then I went to the Carville experience, which is the U.S. Public Health Service experience, which is the major way Americans have legally obtained thalidomide in the United States. There the experience of the database, which we had actually 17 years worth of data, showed it was efficacious by various measures.

I then talked about our reanalysis of the medical records from Carville, which looked at Dr. Hastings' experience, which confirmed that short-term therapy was efficacious for healing lesions and stopping fever.

Finally, I glossed over the extensive literature, which is unanimous that this drug is efficacious.

I'd like to now change our attention towards safety.

Again, our safety database basically is composed of three types of data. The first is the PK studies, which were performed by Celgene. The next is the experience with ENL, and the third is for the use of thalidomide in non-ENL complications.

Now, I would like to summarize our conclusions, before I go into the data, very briefly.

First of all, despite the multiplicity of manufacturers and formulations out there, what we are finding when we went through this database is the frequency and type of adverse events noted were independent of manufacture and formulation. Celgene's drug is no different than anybody else's drug as far as causing adverse events. We found nothing unique.

The most frequent adverse events that we noted, that are noted in ENL trials, are sedation, rash, and constipation. While peripheral neuropathy can occur, it is an infrequent occurrence -- usually occurring in less than 1 percent of patients with ENL. Furthermore, no drug-related serious or adverse events have been described in the ENL studies and the published literature. And that is quite a strong statement, but I am going to show you the database, which is quite large.

When we look at non-ENL trials, the situation is similar, but different. Again, sedation, rash, and constipation are the most frequent adverse events, but now peripheral neuropathy plays a role and, in some respects, a major role. But also you find that disease-related adverse events also were quite frequent. Because, oftentimes, thalidomide is used as a drug of last resort for desperate patients with desperate disease, and so it is not unusual to find adverse events coming in.

Granulocytopenia has been noted more frequently in HIV trials, and I'll talk about that a little bit later.

Furthermore, since 1965, when Dr. Sheskin publicized the fact that this drug works for ENL, in no clinical trial, under no controlled condition, has fetal malformations or fetal exposure been reported.

The data sources. As I said, there are three of them. They are the PK studies by Celgene. We now have data on 83 patients. The ENL trials. We have information on over 3,100 patients. But if you go in the published literature, it gets even larger, because of that large Hansen's disease survey.

Of the ENL trials, we have data on 23. If you look at the non-ENL trials, for all the other indications, we are talking about over 2,200 patient exposures, of which 231 are in HIV trials conducted by Celgene, and 671 for other indications on physician INDs, emergency INDs, and other small trials which Celgene is conducting. And then, the published literature, which is composed of 93 studies from which we could glean safety information on 1,315 additional patients.

Going into the PK studies, again, no serious adverse events or severe adverse events were noted in these studies. The most frequently reported symptoms were dizziness, somnolence and headache. HIV-positive subjects

also complained of confusion, and symptoms were more frequent at higher doses.

One subject did discontinue the study because of an adverse event. And, again, now, this is an adverse event which is consistent with the FDA rules. This patient had an upper respiratory tract infection and pharyngitis, and therefore dropped out of the study. It was not felt to be drug related.

On the other hand, there were some changes in vital signs noted. In healthy human volunteers, a 5 millimeter mercury drop of blood pressure was noted in seated and standing systolic blood pressure and standing diastolic blood pressure. These were not clinically significant.

In HIV-positive subjects, mild orthostasis was most marked for 4 hours after ingestion and could manifest itself as feeling a little light-headed or dizzy.

Two healthy human volunteers, in a study which went up to 400 milligrams, did develop orthostatic hypotension at the 200-milligram dose. These episodes were not prolonged, and both patients were able to walk out of the clinic in a non-orthostatic state.

No other clinically significant ECG, laboratory, or physical findings were noted in this study.

I'd like to now turn our attention to the ENL

studies.

If you look at the three large experiences, where we have the data on safety, you have the two Celgene studies, encompassing 23 patient exposures, and the Carville experience. The interesting thing about the Carville experience is that we have data for at least 6 months on 1,387 patients, and for over 2 years on 377 patients.

In the Philippines study, which I described earlier, again, a 7-day treatment, with either 100 milligrams or 300 milligrams a day of thalidomide, followed by a taper if you respond. 10 of the 17 patients, where we have been able to evaluate safety, had an adverse event, at least one. No AE's were judged to be severe, and the most frequent AE's were somnolence -- it is still a sedative -- rash and vertigo. The rashes were not felt to be severe.

When we looked at E-001, which is a U.S. ENL study, which has recruited 6 patients so far, 5 of the 6 had AE's. Again, none severe. The most common AE's were fatigue or asthenia, arthralgias in 2, fevers and chills in 2.

When we looked at the Carville experience, 1,387 subjects evaluated over a 17-year period, 279, or 20 percent of the people, had adverse events. Approximately half of them had more than one adverse event. The most

frequent adverse events were somnolence, constipation, peripheral edema, which also can be an effect of ENL by itself, fatigue, dry skin, dizziness, and then, finally, you get to paresthesias, which is the first evidence of peripheral neuropathy.

When you look at why patients either discontinued therapy or had dose reductions in ENL due to adverse events, in our studies, there were none. In the Carville experience, of the 1,387 patients in the 17-year experience, only 2 people were noted to discontinue therapy due to an adverse event. 1 person had peripheral neuropathy after 7 years, and the other for dizziness, but the patient was also taking rifampin. And when rifampin was discontinued and the thalidomide was discontinued, the patient no longer was dizzy, and the patient was able to then successfully be placed on thalidomide again without this problem.

When we look at the published literature, a few themes emerge. The first is that clinicians realized very shortly after beginning therapy on a large number of patients that you shouldn't give the drug during the day, because it's a sedative. Give it at night as a sleeping pill. So, the dose was changed because of that.

There have been dose reductions consistent with the adverse events I just mentioned -- somnolence, some

because of peripheral neuropathy, and constipation. I should just mention that constipation and abdominal pain -- this dose reduction often occurred in patients who also were receiving clofazimine.

There are four discontinuations. One for intestinal obstruction in a patient who also was on clofazimine, one for exfoliating dermatitis, and two for anorexia and fatigue.

When you look at neuritis in patients treated with ENL, you find that, in our studies -- and, again, the n is only 23 -- but there was no cases where the neuritis was noted to worsen.

In the published literature, there is no case of neurotoxicity mentioned. And in the Carville experience, there were 18 episodes described among the 1,387 patients. However, some of these episodes are redundant and occurred in the same patient.

As far as serious adverse events, we had none in our trials.

In L-002, there was only one death noted in the electronic case report form. Now, I will just say parenthetically that when you follow large numbers of patients over a 17-year period, there will be deaths. But talking to Dr. Yoder and others, it's our impression that any patient who may have died was off drug.

If you look at the published literature, there were three deaths. None were on thalidomide at the time of death.

Moving over to other indications. If you look at an AIDS wasting trial that we performed, patients were randomized to either placebo or two doses of thalidomide. The only adverse events which were more common in the thalidomide group than the placebo group were somnolence, neutropenia, dizziness, asthenia, and headache.

In an open-label AIDS wasting trial involving 113 patients, the most common adverse events were leukopenia, diarrhea, peripheral neuropathy, rash, fever, pneumonia, and somnolence again.

I'd like to just make one point about leukopenia. Most of the patients in the AIDS trial start out with very low white counts, and therefore they then dipped into clinically significant range. When you saw leukopenia in the literature for ENL, patients would go into a technically low range, but not into a clinically significant low range.

I'd like to now show you this study, which was performed at Rockefeller, in which patients developed fever, rash, somnolence, constipation, dry mouth, perioral numbness, which is peripheral neuropathy, and tachycardia. This is Chemie Gruenenthal's drug, not our drug. The other

studies were our drug. The types of adverse events seen were the same.

When we looked at our emergency use of thalidomide -- this slide is slightly old -- but at that point we had about a fourth patients were women, and they were given the drug for various indications, usually at the end of the disease. Again, it is a drug of last resort for HIV wasting, aphthous ulcers, graft versus host disease, cancer, Behcet's syndrome, both discoid and systemic lupus, and prurigo nodularis.

And we have just updated this last night. The U.S. experience is that 528 people received drug. And these are the most common AE's: constipation, peripheral neuropathy, rash, numbness, xerostomia, tingling, et cetera.

Now, if you assume that there is no overlap, that each person reported is a different patient, peripheral neuropathy becomes the most common adverse event. There it's running at around 6.8 percent, as opposed to 2.5, which is in this figure.

If you look at our study, which looked at rheumatoid arthritis, which used our drug, drowsiness, constipation, dry mouth, rash, and leg swelling were the most common adverse events.

Another study performed with our drug showed

somnolence, change in alertness, malaise. And this was probably one patient who had both upper and lower neuropathy.

If you look at the entire published literature, where you can glean adverse events, that is 1,315 patients. The most common adverse events that occurred -- again, different formulations of the same manufacturer and many different manufacturers -- somnolence, constipation, increased appetite and weight -- which may be an adverse event to some, but in others would be a good thing and this may be a subject of a future hearing -- rash, dry mouth, neuropathy, dizziness.

When you look at discontinuations or dose reductions, you find that the type and prevalence of the adverse event profile is the same reason as to why people discontinue or have dose reductions. And in these patients, it is for rash, peripheral neuropathy, sedation, hypersensitivity, and also disease-related adverse events. Again, these were very sick people.

Of those people who died, none of the deaths were attributed by the treating clinicians as being attributable to our drug.

In our non-ENL-sponsored trials, all SAE's were deemed to be AIDS-related. In the AIDS wasting trial, there were 40 events of 103 patients. In the open-label

AIDS wasting trial, 44 events in 28 patients of the 113 patients, and in an AIDS diarrhea study we are conducting, only 1 in 15 patients.

But, of note, of these 95 adverse events, 12 were for neutropenia. These people started out with very low white counts, and it got lower.

Anecdotally, I will tell you that there was one patient who derived so much benefit from the drug that, despite a white count below 750, the patient insisted on being treated. The patient would go on thalidomide holidays to allow the white count to go up above 1,000. And, finally, the patient was treated with a colony stimulating factor and was able to be treated both with thalidomide and not go off the drug and maintain a white count above 1,000.

There have been no episode of sepsis that we are aware of associated with a low white count on a patient on thalidomide.

As far as deaths, there have been 20 deaths for non-ENL studies conducted by us. None were felt to be related -- all were felt to be related to the underlying disease.

In our emergency use and compassionate use IND program, in both the U.S. and Canada, there have been 22 deaths. And all were deemed to be secondary to the

underlying disease. And the deaths were basically in patients with graft versus host disease, cancer, and AIDS.

As far as laboratory abnormalities, we only really found one. And that is leukopenia or neutropenia, which, in the ENL studies, is between 0 to 8.4 percent, and in our non-ENL studies, in Celgene's studies, it is about 20 percent. In the Chemie Gruenenthal study, it was about one-third. And in the literature, it is about 2 percent.

As far as the potential for drug abuse, overdose problems, and drug interactions, there have been no reports of drug dependency to thalidomide. There have been no case reports of death occurring from an overdose. And this goes all the way back into the 1950s when the drug was being used as a sedative, and people were killing themselves with barbiturate overdoses.

There have been no known drug interactions, and this was discussed earlier.

And as also discussed earlier, there is no effect on the cytochrome P450 metabolism of drugs, or these enzymes do not really affect the major metabolism of thalidomide, either.

So, I'd like to summarize the safety aspect of this presentation by saying that the ENL and non-ENL adverse events are complementary but not identical. In ENL, you find sedation, constipation, and rash as the major

adverse events, followed very rarely by peripheral neuropathy.

On the other hand, for non-ENL indications, again, sedation, constipation, and rash are prominent, as well as peripheral neuropathy.

In HIV, you find granulocytopenia is more a problem, because patients usually start with a lower granulocyte count to begin with.

And then the other AE's are mostly disease-related.

Discontinuations due to AEs and dose reductions mirror the AE profiles that occur in these two conditions, as far as the reasons. And, as I said, since 1965, in patients who have been treated under clinical protocols, there have been no reports of fetal exposure.

Now, I just want to end by saying that when you consider this evidence, Celgene feels that we could have the following indication if you agree with us. We propose the following indication: basically, that thalidomide is indicated for the acute treatment of erythema nodosum leprosum, or ENL, as well as the maintenance therapy for prevention and suppression of ENL recurrence.

We believe that the drug will be efficacious and should efficacious in the acute setting, for 100 to 200 milligrams per day, taken at bedtime, and that, for severe

ENL, to us higher doses.

Thank you very much for your patience and consideration.

DR. McGUIRE: Thank you, Dr. Zeldis.

It very frequently occurs that we have too much information and not enough time. So, we are a little short on time right now. I am going to change the program around a bit and go directly to Dr. David Cornblath, Professor of Neurology at Johns Hopkins, who will address the issue of neuropathy.

Following Dr. Cornblath, we will have a brief break, and then Dr. Bruce Williams will present his data.

Dr. Cornblath.

DR. CORNBLATH: Thank you very much, Dr. McGuire.

I am going to just make three extremely brief points, so that we can finish at 11:15. If I could have the first slide.

Let me just remind the people who do not remember from the last time I had the privilege of presenting to this group, I am a neurologist at Hopkins, interested in neuropathy, and I was asked a year and a half ago or so by Celgene to look at the neuropathy issue as regards to the literature.

I just want to point out two things -- three

items from before, and bring you up to date.

First of all, as we think about the neuropathy that occurs with thalidomide, there are several epidemiologic features to keep in mind, and particularly as we look at short-term studies. And that is that, in general, symptoms of neuropathy begin anywhere from 2 to 20 months after the drug and, in general, it requires a mean of about 37 grams of drug. So, if you are talking about somebody taking 100 milligrams at nighttime, you can see that it is going to take close to a year or more to develop neuropathy, and that the total dose in people who get neuropathy has a mean of about twice that.

What is quite interesting from my perspective is that not all people are affected under similar conditions. So, if one looks across the spectrum of the literature and sees similar studies giving similar doses, the range of neuropathy is actually quite remarkably different. As has been mentioned before, at least in the published literature, it appears as though neuropathy has not been reported in patients with leprosy. And overall, the incidence of neuropathy occurring in those given leprosy is unknown. That is point one.

Point two is over last weekend I had the opportunity to review 17 of the case report forms from the study we have heard about, the 003/P, and I particularly

concentrated on what the treating clinicians said about neuritis, nerve enlargement, nerve pain, paresthesias, et cetera, and I am lumping them all together under the term "neuropathy." And in the 17 that I reviewed, 15 were abnormal at baseline, and only two of the patients were normal at baseline.

When one looks, then, at the end of the study, one sees that the two normals remained normal, but of the ones that were abnormal, about half of them improved in some characteristic of what was recorded as neuropathy. That's either nerve pain, neuritis, nerve enlargement, or nerve tenderness.

It is not on this slide, but I can say that participants in this study were asked on a daily basis for the first week, and then on a weekly basis thereafter, if they had numbness or parasthesias, in other words, what would have been the first symptoms of neuropathy. And, not unexpectedly, none really had these with any persistence. The occasional subject would have them for one day.

The third thing I would like to mention is just a personal experience with Dr. Hugo Moser at Hopkins. We have been, now, looking at study in which Dr. Moser has been giving either thalidomide, beta interferon or placebo, or the combination of thalidomide and beta interferon to young boys with life-threatening and immunologically active

adrenoleukodystrophy. And, at least as we have been monitoring that study with careful clinical and electrodiagnostic serial studies, we have not detected neuropathy in a study that is now moving into its second year.

So, I think that, overall, the view is that, in low doses for short periods of time, neuropathy is something that, in essence, we are not going to see much of, because it takes a much higher dose, to be given over a longer period of time. And that, under controlled situations, if one prospectively looks for neuropathy -- one can detect it in the literature -- it is quite clear that if one detects the beginning of neuropathy, that is the time to stop the drug. And you are not going to end up with bad, long-term side effects.

Thank you very much.

DR. McGUIRE: Thank you, Doctor. Will you be here after the break, Dr. Cornblath?

DR. CORNBLATH: Yes.

DR. McGUIRE: Let's have a break until 11:30.

(Recess.)

DR. McGUIRE: Could I invite the advisory committee to have a seat?

Dr. Williams. We are now going to hear from the sponsor, Dr. Bruce Williams.

If people could be seated, the advisory committee is convened.

We will now hear from Dr. Bruce Williams, who will speak on the sponsor's approach to fetal exposure prevention.

Dr. Williams.

MR. WILLIAMS: Good morning. I would like to thank the agency and this committee for giving Celgene the opportunity to present its plans for preventing fetal exposure in the event that our NDA were to be accepted.

As was said, my name is Bruce Williams. And I have been working for the last several months -- a year or so -- with a heavy focus on exactly this issue. Celgene recognizes that one cannot talk about the introduction of a product like thalidomide, and specifically about thalidomide, without at the same time talking about how one can manage to make this drug available to those patients for whom it has been demonstrated to be effective, while at the same time minimize the very well-known and very significant risk of teratogenicity. And to that end, I will present our proposal.

The objectives of our proposal are, first and foremost, to limit the risk of fetal exposure and any possible resulting birth defects. To do that, by supporting appropriate use of the drug and to ensure

positive evidence of universal compliance.

It is also important, we believe, to facilitate appropriate access. As has been mentioned, there are a variety of historical sources for this drug, both through unregulated and regulated channels. We believe that it's very important that while the program, first and foremost, be capable of assuring that the first objective is realized, that it must do so in a manner that does not in any respect encourage unregulated availability of the drug.

We recognize that there may be some models in the marketplace today which could serve as at least a starting point in our thinking as we develop this program. Two of them came to mind that I would like to just speak very briefly to, to indicate why we feel that they are relevant models, but also where we feel they may not go far enough for this particular circumstance.

The first is one that this committee, particularly, is very familiar with. And that is Roche's Accutane, used to treat severe acne, and known to be a human teratogen. After the knowledge of the extent to which Accutane could result in birth defects became widely understood, Roche, working with public health officials, the agency, this committee, and others, developed what they refer to as their pregnancy prevention program, a program of education, informed consent, recommendations for

contraception, birth control, counseling, and a voluntary registry to track compliance with the program and outcomes to the program.

The program also included a repackaging of Roche's product, from available in bottles to available in a carded blister, where the card provided a lot of opportunity for reminders of the relevant warnings and instructions to patients to be intimately associated with the product.

All of this seemed good, but there were several elements that we questioned whether they were sufficient for the challenge that we saw with thalidomide. Firstly, the surveillance registry was not mandatory, and therefore it's not really clear what the effectiveness of the Accutane program is in the real world. It's not even clear what proportion of patients who take Accutane in fact are participating in the registry survey, although estimates of that have been made.

Secondly, there is no mechanism to ensure that when a prescription shows up in a pharmacy, that the patient has in fact participated in all of the support programs that have been provided by Roche to the dermatology community.

That caused us to look at other programs.

Novartis, previously Sandoz, introduced

Clozaril, an anti-schizophrenic drug, some years ago as a significant improvement, from an efficacy perspective, over available therapies for many patients. However, it had a life-threatening side effect of agranulocytosis that occurred in a small proportion of the patients.

Sandoz developed a program that, from a practical perspective, ensures that patients have had their white blood counts taken prior to the dispensing of their next prescription, and that those white blood count numbers are in the appropriate range.

In looking at how Sandoz structured this system, we began to see that by taking elements from the Roche program, elements from the Clozaril program and other unique elements, we could create a system that really would be state-of-the-art, represent a significant step, we believe, forward in the ability to make drugs like thalidomide available to patients who need it, while at the same time providing a very high margin for protection.

Components of the program would include education -- not only patient education, but also education aimed at health care professionals from a CE and CME perspective included.

Counseling, with a referral option. If a prescribing physician does not feel capable, competent or willing to provide adequate contraceptive counseling,

Celgene would make that available.

A regimen of pregnancy testing for women with childbearing potential.

Informed consent.

Managed distribution that ensures that in fact these steps are occurring before the drug can be dispensed.

And, lastly, a mandatory outcomes registry survey.

And I will talk about each of these elements in a bit more detail as we move through.

We also, though, recognize that while one could look at models that had been in place in the past, it was important to talk to the folks who had prescribed the drug, dispensed the drug, and might take the drug, as well as other interested parties, to ensure that the program being developed was one that really would work and have the outcome that we all, I think, share as an objective.

We held focus groups with physicians who might prescribe the drug, pharmacists who would dispense it, and patients who might take it. We wanted to ensure that the materials that were in development were in fact understood by patients, were clear; that patients recognized the risks that they were taking on if they agreed to this therapy and their responsibility in helping to manage those risks; that pharmacists could work with the system in a manner that was

not so inconsistent with existing pharmacy practice that it just was not going to work; and for physicians, the same thing, that this was a program and proposal that could work in medical practice today.

We also have gotten input from a wide range of public health circles, including the Centers for Disease Control, of course this agency, academic public health officials, and officials including organizations like the Organization of Teratology Information Services. We have worked with patient advocacy groups, disease-specific, as well as larger umbrella groups, such as the National Organization for Rare Diseases, and we have had very significant and, from my perspective, extraordinarily valuable dialogue with the Thalidomide Victims Association in getting their input as to what an effective and appropriate distribution system should look like. They have even, to date, had an opportunity to review some of the support materials that we would intend to use with the program.

Women's health organizations were consulted specifically for many of the same reasons that were mentioned in some of the public comment this morning. We know that women's health organizations want women to have access to effective therapies. We also know that they are very concerned about the health and safety, not only of the

women who are patients, but of the unborn who those women might bring into the world.

And with that input, let me get straight into the program.

The program starts in a physician office. A physician, who has been fully informed and educated on the program, has made a decision that this patient should be considering thalidomide as a therapy in the regimen. Counseling would occur, facilitated by materials provided by us, on the risks and benefits of using this therapy -- all of the risks and benefits, particularly the teratogenic effects, but others as well.

The patient and the physician would engage in an informed consent discussion, leading to the signing of an informed consent document, where each of the major points on that informed consent document are initialed by the patient, in addition to simply signing at the end. This informed consent would focus not only on the risks, but also on the patient's responsibility and the actions the patient would be expected to take in managing those risks, and would also represent the patient's consent to participate in the registry.

When this has occurred, a prescription could be written for no more than 28 days, or 4 weeks, of therapy at a time, with no automatic refills. And I will show how

that works at the pharmacy level in a moment.

But we feel that it is very important that the prescription not be fillable, written as many traditionally are, a month's supply with six automatic refills; that there needs to be a check back to the prescriber with each and ever subsequent dispense that that patient would receive, providing an opportunity for the appropriate supporting counseling, pregnancy testing, neurologic monitoring, and any other appropriate follow-up that would need to happen.

Previously, I was talking about all patients. We believe it's important that all patients, men and women, participate in the program. Preventing fetal exposure is not simply the responsibility of those patients who are reproductively capable, but, in fact, is the responsibility of any patient who might take this drug out of a pharmacy into an uncontrolled home environment, who needs to know to ensure that the drug is kept secure, is not shared, and is not consumed possibly by someone for whom it was not prescribed.

For female patients, contraceptive counseling will also be an important part of the program. And as I indicated, if the prescribing physician does not feel competent, capable, or comfortable providing that counseling, Celgene will facilitate a referral to a

gynecologist who would be.

Pregnancy testing would be required, and patients would be asked to delay therapy until their next period or the initiation of effective contraception. And in fact, as was mentioned earlier, rarely is the condition for which thalidomide is likely to be prescribed, including ENL, so life-threatening that waiting until effective contraception has been established would not be realistic.

The pharmacy is particularly important because, again, as important as the physician level is, it is critical to know that a rural physician who may not have been on our radar screen, who may simply be aware that the drug was approved and try to write a prescription, cannot get that prescription filled without participating in the program. What we propose is that only pharmacies who have registered and agreed to the following would be able to purchase the drug. An order coming to purchase the drug from an unregistered pharmacy will not be filled.

Pharmacists' registration includes agreeing to dispense no more than 4 weeks at a time in the original packaging. That is critical, because the original packaging, as I indicated, is being designed to ensure that the warnings and instructions to patients are an integral part of that packaging. That the initial dispense occurs only with an informed consent, and that subsequent

dispenses occur only with a new prescription. And that all patients are registered into a system that will allow us to be able to match patients to whom the drug was dispensed with the patients' participation in the registry, which I will describe in a moment.

Another important piece here is that an additional copy of the informed consent will be sent back by the physician's office to the group managing the registry when the patient initiates therapy as an additional check that we are actually getting registry participation.

For the registry, we have been working with the Slone Epidemiology Unit at Boston University -- Allen Mitchell's group particularly -- to develop the thalidomide registry. We chose this group because they have had a lot of experience with Accutane, they've understood what works well, and they've got a good perspective on how things could be improved.

All patients will participate. It resolves one of the issues that has been raised in a number of circles about not knowing the end for Accutane. And responses will be confidential to the immediate health care team and the investigators at Boston University.

Female patients will complete the survey monthly, and male patients will complete the survey no less

frequently than ever 3 months and at any visit to the physician office. The objectives of the registry are twofold and I think, very importantly, to track compliance with the program because it provides us with a continuous feedback loop in understanding how effective the various elements of the programming are working, what level of compliance we are getting, whether there are pockets or individuals who may be complying less well than all of us would expect, and provides us the opportunity to go back and take corrective action.

It also, of course, would provide as an objective the ability to identify and track any reported fetal exposures.

In summary, we believe that we have created a unique program, a program that can provide a very high level of confidence that we are tracking all of the patient exposures to this drug, that we have provided every patient, prior to receiving the drug, with an opportunity for good education and informed consent, that the drug is being prescribed and dispensed by clinicians and pharmacists who understand what they are taking on in prescribing and dispensing this drug, and will in fact provide an opportunity to make this drug available to those patients who need it, while at the same time providing a high level of protection of the public health.

Thank you very much.

DR. McGUIRE: Thank you. Remain there, and we will have a few questions directed toward you. Then, we really did not have an opportunity to question Dr. Zeldis, so we can direct questions to both of you.

Dr. Bergfeld has a question.

Could we have the lights, please?

DR. BERGFELD: Thank you. I think that is very interesting, this program that you are presenting. And having been in on the Accutane development of their pregnancy protection program, I think this exceeds their efforts, and I commend you.

I would like to ask you a question, though, about the M.D.s. And you mentioned in your presenting remarks about education of the patient, doctor, and counseling available to the patient for birth control. I am concerned about the education of the physician, and perhaps a similar method of registry for the physician that is being imposed on the pharmacies could be employed with the physicians. Is that under consideration?

MR. WILLIAMS: Yes, it is certainly under consideration. And I think that one of the pieces of feedback that Celgene is certainly interested in today is effective methods for doing that.

We believe that certainly any physician

prescribing this drug needs to understand all the issues associated with prescribing the drug, and consciously accept their responsibility to move forward and in fact prescribe the drug.

We will know all physicians who are prescribing the drug, because they will not be able to prescribe it, number one, without having our materials -- which they will have to get from us on request, and, number two, we will know them because when the drug is dispensed at the pharmacy level, the information that goes into that part of the tracking system will include prescriber information.

But I do agree that methods to attempt to confirm the physician's knowledge and acceptance would be useful. And a question or concern that we have is the degree to which the manufacturer can reasonably be expected to be in an accrediting role, in the sense that that typically occurs by governmental or medical society organizations. Any further dialogue on that subject would be very helpful to us.

DR. BERGFELD: What I would like to recommend is that registry for the physician include that they have signed off on an informed consent that they have been informed about the information, they have read it, and they agree to participate in that manner. It does not have to be anything in depth further than that.

MR. WILLIAMS: That is reasonable.

DR. BERGFELD: I would like to ask a second question, and that is to deal with the packaging. Are you going to employ similar packaging that was developed for the Accutane package?

MR. WILLIAMS: Yes. We believe that the general concept of that package, at least in the big picture sense, is very effective. The package includes an opportunity for some direct warnings, some clear bullet points on the back that summarize the major issues.

There are a couple of things that we believe, though, need to be done differently. We are a little concerned that line drawings do not necessarily provide the appropriate understanding of the severity of the risk of birth defects. And it would be our proposal that a photograph of an affected infant be used in conjunction with the packaging rather than, for example, a line drawing as is used in other circumstances and in other situations.

But, in concept, adjusted of course for the differences between Accutane and thalidomide, the packaging concept is similar.

DR. McGUIRE: Mrs. Cohen, you had a question?

MS. COHEN: Yes, I have a few questions, if you can help me, please.

In the real world, a lot of us are or will be

controlled by HMOs. Are you certain that HMOs are going to even prescribe thalidomide?

I am also concerned about the off-label use of this.

And I am also concerned about your questionnaire. One of the suggestions I would make is, you have a questionnaire you have for the women to fill out, informed consent, and the men. I would strongly urge that both men and women read the whole thingbecause I think each of them should know the problems of the other, and therefore they should sign off on both because it is two people, actually, as far as I know.

(Laughter.)

MR. WILLIAMS: A point well taken.

MS. COHEN: But I am concerned about patients who are in an HMO -- and I have had a lot of discussions with a lot of friends who are physicians who are being forced into dealing with patients from HMOs. They do not have any time. They have to see so many people within an hour. This takes time. It takes intelligence. It takes understanding. And I wonder if this is the real world that people are going to find.

And I am concerned about the off-label use of thalidomide, to tell you the truth, very concerned.

MR. WILLIAMS: Let me address managed care, as

best as I can, first.

In fact, the Accutane experience, in some respects, may be a useful one as it relates to managed care. Managed care, one of its objectives recently, has been to try to keep patients within the primary care setting and away from specialists as much as possible. And one might think that managed care would therefore be discouraging of primary care referrals to a dermatologist for acne if the primary care doctor could be expected to manage the condition.

I think because of the issues associated with Accutane, it is our understanding that managed care, in fact, encourages primary care docs within their system to refer to dermatologists to receive Accutane. There are probably exceptions to that, but when one looks at the prescribing data on Accutane, the vast majority of it is coming from dermatologists still.

We also will be requiring that managed care organizations, especially those who purchase and dispense drugs themselves, will have to be able to comply with our system. If they are going to purchase and dispense the drug, they will have to register their pharmacy. Their pharmacists will have to ensure that the program integrity, at least at that level, is still being maintained. And the managed care organization would, of course, need to ensure

that the doctors that they are permitting -- because they have the ability to do that -- to write for this drug are doctors who will be able to do it responsibly.

I share your concern because I see medicine moving that way, where good, quality patient/doctor time is difficult. But I can tell you that in speaking with a large number of physicians who might write for this drug at some time in the future, they take this drug very seriously and are going to be, I think, very reluctant to write for it unless they know they have an opportunity to ensure that they and the patients are going to be able to manage it responsibly.

I will speak to uses outside of the label in the sense that we are aware and, in fact, we are even conducting some of the studies that might lead to other uses of this drug beyond that which is being discussed today. And for that reason, we believe that it is very important that the program be designed in a way that would capture all use of the drug, and that no prescription could be written for the drug for any condition without the patient being captured within the system.

DR. McGUIRE: Mr. Williams, your view of the registry is that it would be a pretty much leak-proof system, that it would not allow off-label usage?

MR. WILLIAMS: No, I am not saying it would not

allow off-label uses. I am saying it would not allow use of the Celgene drug product without being captured in the registry.

DR. McGUIRE: But the registry is an ENL registry. Correct?

MR. WILLIAMS: The registry is a thalidomide usage registry.

DR. McGUIRE: Well, that is quite different.

MR. WILLIAMS: Yes.

DR. McGUIRE: If there are somewhere between 20 and 200 cases of ENL a year, are pharmacies going to be interested in participating in another piece of bureaucratic registry?

MR. WILLIAMS: We do not expect that a high proportion of the pharmacies in the United States today -- there are roughly 60,000 of them -- will in fact be involved. In fact, we expect that number to be really quite small. But we want to ensure that no pharmacy can order the drug without having agreed to and registered and is participating. But we fully expect that it will be a very small number of pharmacies.

DR. McGUIRE: Dr. Mindel.

DR. MINDEL: The informed consent will state that the drug is for ENL?

MR. WILLIAMS: The informed consent, as it is

drafted and I believe provided in your read-ahead packages, at this point, again, indicates that you and your physician are considering the use of thalidomide. This is what you need to know and agree to before you use it.

DR. MINDEL: And the informed consent will be signed by males and females?

MR. WILLIAMS: That is correct.

DR. MINDEL: And required by the pharmacist by males and females?

MR. WILLIAMS: That is correct.

DR. MINDEL: The only loophole I see, then, is that someone could sign it and use the drug for something other than ENL. Why doesn't the informed consent specifically state it's for ENL?

MR. WILLIAMS: I'll let Steve manage that.

DR. THOMAS: I would welcome the opportunity of actually making at least an initial response to actually what is a very important question. If Bruce or anybody else on the team thinks they have actually more to add, than I'll be hoping to hear from you.

I think it's important to realize that what we're talking about here is a draft. The approval of the drug is actually dependent on, obviously, the recommendation of the committee today and actually a variety of discussions which will occur after that point,

inside the agency. Only after an approval has actually been deemed acceptable, if that is the decision, are we going to get into the position whereby the overall restrictions that the agency is imposing on the company are incorporated into all of our documentation?

If that is what the agency is actually demanding of us, then, obviously, we will have to comply. I think Bruce's point is that in an informed consent, in this program, what we are trying to do is to provide a broad base, which if the drug is approved in its initial indication, if it is then actually approved in what is likely to be a broader indication actually than AIDS wasting, that we do not have to re-engineer that system in a way that is actually going to multiply the amount of paper on an indication-specific basis.

However, all of that is with the caveat that the drug has not yet been approved, and the agency has not had an opportunity actually to provide an input as to what it wants to see in the labeling, if the labeling is a question that our company has an opportunity of providing an input into, i.e., after an approval process.

Do you want to add anything else, Bruce?

MR. WILLIAMS: No. I think Steve is absolutely right. All of this is still subject to further discussions with the agency, with the input that they are receiving

today and from other sources.

In addition, the program was designed to reflect at least current clinical practice, where approved drugs can be prescribed by medical professionals within both the approved indications, as well as other areas wherein either the support literature or the medical judgment the drug may be useful. And from that perspective, we felt it critical that there not be an opportunity for use of the drug to occur outside the system.

DR. McGUIRE: Mr. Williams, thank you very much.

MR. WILLIAMS: Thank you.

DR. McGUIRE: We have one more question for Mr. Williams?

DR. MOORE: I have a question concerning actually the last discussion.

Are you envisioning in your system a notation of why this drug was used in a patient, so that that will be able to be looked at also?

MR. WILLIAMS: Yes, absolutely. In fact, Dr. Mitchell was just nodding his head. One of the data elements in the registry would in fact be an opportunity, or a requirement, that the prescribing physician indicate the indication for which the drug was prescribed. We feel

it is important, to the extent that it gets prescribed beyond whatever the labeled indication is, that that is known and that the experience base can be monitored on that variable as well.

DR. McGUIRE: Yes.

DR. MATHEWS: I had one particular question about the requirement that males use condoms with every episode of intercourse. What is the evidence that led to that recommendation?

DR. THOMAS: The evidence that actually led to that was it's better to be actually very safe than very sorry. At this moment in time, we have not had an opportunity to absolutely discount the chance that there may be even small levels of the drug in the semen. That actually being the case, it is entirely appropriate that until we have undertaken a study where we have categorically shown that that is not the case, that we engineer a program that avoids that problem if it actually exists.

The other thing is, if you are asking it of women, why shouldn't you be asking it of men?

DR. MATHEWS: Well, I think that there are biological reasons why people treat the sexes differently.

But, more importantly, to my knowledge, and correct me if I am wrong, that is not currently a

requirement of informed consent documents for clinical trials using thalidomide in males, is it?

DR. THOMAS: It is, absolutely. Well, all of the clinical trials that we have actually currently ongoing -- and I have experts here who I am sure will actually contradict me if I am saying something stupid. In all of the trials which are currently ongoing, it is a requirement that actually that occur.

DR. McGUIRE: Yes, this will be the last question of the morning session.

DR. CRAWFORD: On the labeling, will there be any mention of the neuropathy as a side effect?

DR. THOMAS: Absolutely.

DR. CRAWFORD: And what will it say?

DR. THOMAS: It will indicate that actually this is a known side effect of the drug. And this is obviously only the basics that I know I would recommend be actually on there. The FDA is going to have its own view. It is a known side effect of the drug.

The incidence in a range of indications is actually variable. It must be monitored. These are the basics. The actually labeling as an endpoint is clearly going to be something, if the drug is approved, that the agency and the company are actually going to want to spend a lot of time on.

All of the known side effects of the drug are going to be incorporated into the label.

DR. McGUIRE: I would like to thank Celgene for the very clear and detailed presentations this morning.

We are going to break for lunch now. We will reconvene at 1 o'clock. And the open public hearing will begin at 1 o'clock.

Thank you very much.

(Whereupon, at 12:08 p.m., the committee recessed, to reconvene at 1:11 p.m., this same day.)

AFTERNOON SESSION

(1:11 p.m.)

DR. McGUIRE: Good afternoon. I would appreciate it if the participants and guests could be seated. We have several oral presentations this afternoon.

Is Christopher Doyle here?

Mr. Doyle, would you come up and use the microphone in front.

Mr. Doyle is the President of the American Leprosy Missions.

MR. DOYLE: Mr. Chairman, ladies and gentlemen, I want to thank you for the opportunity to be here today to address this panel and to be part of this important discussion. My name is Christopher Doyle. I am the President of American Leprosy Missions, which is a not-for-profit international medical organization, based in Greenville, South Carolina.

I come before you today as both a spokesperson and an advocate for the millions of people worldwide who are affected by Hansen's disease, or what is more commonly known as leprosy. I do not necessarily come here as an advocate for any particular therapy or company. I have not been paid by Celgene in any way, shape, or form to appear today.

Rather, I am here in support of any and all

research which will lead to the availability of new therapies, which will ease the suffering and improve the quality of life for all people with leprosy.

I have also come here to present some facts for consideration. For over 90 years, American Leprosy Missions has been involved in the lives of some of the most marginalized and ostracized human beings in history. To most, these are the unknown and the forgotten in a very literal sense.

When we talk about people with Hansen's disease, we find that one of two things is routinely true. Either people don't know leprosy still exists or, if they know it exists, they certainly don't know that it is curable. It is this unfortunate reality that has, throughout history, led to the segregation and, in many cases, banishment of people with leprosy.

Part of our mission is to educate the public about people with leprosy -- people who have and deserve a place in our world. Let me just state a few facts -- and I understand this morning -- I was not here -- we had a little controversy about figures, but I am going to state some anyway.

Leprosy affects millions of people worldwide. The WHO estimates that between 1 million and 2 million people either are on treatment or are in need of treatment.

Registered cases number close to 1 million worldwide. For the past 5 years, at least the number of new cases worldwide has averaged almost 600,000 per year. That amounts to 12,000 new cases per week, or 65 per hour. Many of those diagnosed are children, and many have a grade 2 disability at the time of diagnosis. We believe this constitutes a public health problem on anybody's scale.

There is an effective chemotherapy treatment for leprosy. The successful implementation of this multi-drug therapy, or MDT, has caused the number of cases to drop from 10 million to about 2 million in a decade. Clearly, this is good news.

However, most of the 8 million who have successfully completed their MDT treatment are still alive. And many of these people suffer from a variety of continuous medical and physical problems, not the least of which is ENL. Admittedly, the exact numbers are hard to come. While we believe we have done a good job tracking cases of treatment, we have not done nearly as well in tracking disabilities and other physical problems.

But our experience on a worldwide basis tells us that ENL constitutes a significant problem that needs to be addressed.

And, finally, our field experience across the world has shown us that thalidomide can be and is an

effective tool for the treatment of ENL. These are the facts, ladies and gentlemen.

As President of American Leprosy Missions, it is my job to speak up for those affected by leprosy, and to push for full access to the best medical treatment available.

It is also my job to ask questions. Is this treatment providing a better alternative over current therapies? Is it readily available? Is it safe and effective? And, perhaps most importantly, will any new therapy work better without adding risk to the patients?

Again, my purpose is not to advocate on behalf of thalidomide. These are the issues as we see them. A lot is at stake, but we view it quite simply -- it really comes down to providing access to the best medical treatment available for a group of people that we care deeply about and for.

As we see it, your task is to examine all available evidence and determine whether the benefits of a given therapy outweigh potential risks. We trust that you will do it as fairly and impartially as humanly possible.

I thank you again for the opportunity to address you today.

DR. McGUIRE: Thank you, Mr. Doyle.

I invite you to stick around for a couple of

days and see if we come close. We'll try.

Is Dr. Holmes present?

Dr. Holmes is representing the American College of Medical Genetics and the Teratology Society.

DR. HOLMES: Mr. Chairman, could I just sort of make the point that each wants to make separately, back to back, because each submitted a separated statement?

DR. McGUIRE: Okay. He is representing them sequentially. It took me a while to catch on to that.

Thank you.

DR. HOLMES: Okay. First, my comments are reflected in a one-page memo that was just handed out to all the members of the committee after lunch, the American College of Medical Genetics.

It may seem strange to you that a genetics society would be standing here, commenting on potential environmental exposures with awful fetal effects, but many clinical geneticists around the country are expected to provide counseling to pregnant women about exposures in pregnancies, so the geneticists, in fact, are often the clinical teratologists. And I am speaking myself as an active clinical teratologist in the Boston area.

We have several recommendations that are listed, and we are particularly concerned that the committee hear from us what they have obviously heard now

today from several groups, that thalidomide be prescribed only by physicians and pharmacists who have completed a thorough educational program and are well informed about the risks of fetal damage. Parenthetically, I would say, we are not particularly impressed with the adequacy of signing a consent form to achieve that.

Second, after the patient has been well informed, only then should she have access to the medication.

Thirdly, that she be on an effective contraceptive.

Fourth, that the packaging itself include visible warnings, as we are very concerned about off-label use, and this would at least mean that anyone who got a hold of the labeled product would again be reminded of the potential fetal effects.

Then, finally, that there be close follow-up of all patients.

There are three closing comments I would like to make on behalf of the American College of Medical Genetics. I think this committee would be well advised to ask those who followed the experience with Accutane what the pitfalls and problems have been. And I would particularly recommend you ask Dr. Edward Lammer to give his observations about the continued unfortunate exposure

of pregnant women and their fetuses to Accutane with devastating effects. Clearly, the Hoffman LaRoche program has its limitations, and he could define what has been observed by him in his prospective study for the last 10 years.

Second, we are very concerned about the off-label use of thalidomide. I think there is no debate that it is happening already and it will continue. I would suggest you bear in mind the experience with misoprostol, which is now, in South America and Central America, one of the most widely used abortifacients, illegal of course, with extensive fetal effects. And it represents the enormous problems with off-label use.

And then, thirdly, I think the committee ought to wrestle with two big issues represented by thalidomide: Can't there be ways to restrict the number of physicians who can prescribe them -- and this would certainly be an example to use, to ask that question again -- and thereby learn from the tragic mistakes of Accutane, misoprostol and, undoubtedly, thalidomide.

So, now, let me turn to the comments by the Teratology Society, which I also represent in which I am also an active member. I will just highlight some comments that are written out in greater detail by Dr. Jan Friedman in the handout you have in your packet.

First, I would point out the Teratology Society was formed in 1960, following the thalidomide epidemic. It is an organization of over 700 members concerned about the causes of birth defects and, obviously, their prevention.

Second, the Teratology Society supports the implementation of a mandatory system of controls on the prescription and use of thalidomide, if it is approved by the FDA.

Skipping down in the second paragraph, we believe that many suggestions considered at CDC workshop, which you will hear about later from Dr. Moore, provide a reasonable basis for a system of controls that will be necessary if thalidomide is released.

The next point, in the third paragraph, the controls on thalidomide must include provisions that require the drug to be packaged and dispensed in a manner that minimizes inappropriate and inadvertent use.

And, then, going to the last page, I think this, again, is important for everyone to hear. We believe that a decision by the FDA to make thalidomide available in the United States inevitably means that some American children will be born with thalidomide embryopathy.

Thank you.

DR. McGUIRE: Thank you very much.

This advisory committee was addressed by

Dr. Lammer in November.

Is Lynn Klein here?

Ms. Klein is the Executive Vice President of the National Organization for Rare Disorders.

MS. KLEIN: Mr. Chairman, members of the committee, thank you for the opportunity to appear before you today.

The National Organization for Rare Disorders, NORD, is a unique federation of voluntary health agencies, dedicated to people with rare disorders. NORD is dedicated to the identification, treatment and cure of orphan diseases, and the welfare of more than 20 million Americans afflicted by these diseases.

I have no financial interest in Celgene, nor has NORD received any money from the company to appear here today.

Since its inception in 1983, NORD has served as the primary nongovernmental source for those seeking information on more than 5,000 rare diseases, as well as referrals to appropriate sources for diagnosis, treatment, and support. In addition, NORD funds clinical research grants, as well as a patient networking program, and seeks to ensure that Federal policies are responsive to the needs of the orphan disease community.

NORD is proud of its achievements, the

enactment and continued reauthorization of the Orphan Drug Act of 1983, and, most recently, the legislation making the orphan drug tax credit permanent. Today's thalidomide application has made its way to you, in part, because of the incentives provided by the act.

All of NORD's activities are made possible through the generosity and continued support of the general public, foundations, corporations, and other interested donors. We at NORD believe that Celgene's application for approval to market Synovir, or thalidomide, for the treatment of leprosy is worthy of the committee's careful consideration.

Few diseases are as horrible or as ignored as leprosy and its sequelae, including erythema nodosum leprosum -- most commonly referred to as ENL. A promising treatment option such as thalidomide, while not necessarily appropriate for every patient with leprosy, is another important part of the ENL armamentarium, one which will bring hope to patients and doctors alike.

We have come to this conclusion only after much discussion and debate. While few can question the efficacy of thalidomide in the treatment of ENL, we all acknowledge the concern about the safety of the drug. All of us must be conscious of what the FDA's own Mary Pendergast stated to the committee last year: Thalidomide has the potential

to do enormous harm as well as enormous good.

NORD brings a special vantage point to this discussion. A few years ago, NORD was recognized by a Federal court's special master to design and implement a patient assistance program for clozapine, a psychotropic substance of great efficacy, but associated with life-threatening hematologic disorders. NORD has developed special expertise in balancing the need for access to effective treatments with the requirement of ensuring their appropriate use.

We at NORD now believe that Celgene has taken exceptional steps to ensure the safe and appropriate use of thalidomide, through its comprehensive program to prevent fetal exposure, which we understand includes informed consent, restricted distribution and a mandatory patient registry, among other components. The sponsor has worked purposefully to reduce the likelihood of fetal damage in subsequent generations.

The sponsor has, we believe, studied and learned from relevant experiences, most especially the restricted distribution programs developed for clozapine and Accutane. Indeed, by consulting with both academic experts and patient advocates in a variety of areas, the sponsor has developed a new standard for the appropriate use of a highly teratogenic substance.

No one can enter into the discussion of the return of thalidomide to the physician's armamentarium lightly or with a degree of certainty that we would all hope to find. We at NORD believe, however, that the discussion should not even begin unless a well-articulated, responsible program to prevent fetal exposure is in place and appears likely to be effective.

In this case, that of thalidomide for the treatment of ENL and leprosy, as well as for any potential off-label use, the company has done its utmost to design an intelligent and well-thought-out plan to protect the unborn. ENL is not a simple, cosmetic problem like acne. It is a crippling, life-altering disease. Leprosy patients desperately need and deserve to have access to this drug.

Thank you.

DR. McGUIRE: Thank you, Ms. Klein.

Cynthia Pearson is the Executive Director of the National Women's Health Network, and she will address us next.

Ms. Pearson.

MS. PEARSON: Thank you. I'm representing the National Women's Health Network, a national consumer organization. We are supported by membership dues from our 14,000 individual and 400 local organizational members. We accept no financial support from manufacturers of

pharmaceutical drugs or medical devices.

In 1961, when the FDA was first faced with the approval of thalidomide, it did the right thing. Thanks to the persistence of Dr. Francis Kelsey, the medical officer assigned to thalidomide, the FDA refused to approve thalidomide until its manufacturer could produce better evidence of the drug's effectiveness. During the delay imposed by the FDA, studies in Germany and Australia found that thalidomide caused serious birth defects, and the FDA's caution prevented a tragedy, at least in this country.

Other countries were not so well-served by their regulatory agencies, and thousands of children were born with birth defects caused by thalidomide. The visible presence in many countries of persons affected by thalidomide have served as a constant reminder of the risks of fetal exposure to pharmaceutical drugs, especially thalidomide.

Now, after more than a generation of thinking of thalidomide primarily as an example of why FDA scrutiny is so important, the FDA has been asked to once again consider thalidomide as a treatment. It will be much more difficult for the FDA to do the right thing about thalidomide in 1997 than it was in 1961, because now the FDA and those of us involved with consumer advocacy

organizations have to consider many layers of issues.

In 1961, the FDA was able to consider the patient's safety and the drug's efficacy and stop there. Now, it appears that the FDA will have to go well beyond efficacy for the patient, and carefully address issues of fetal protection, respect for the reproductive health decisionmaking of women, and the special needs of minors. This process is sure to be difficult.

First, the committee must consider the evidence for the effectiveness of thalidomide in treating leprosy-related conditions. If the committee finds that thalidomide is effective, then the next issue to be considered is how to make thalidomide available in a way that protects against fetal exposure. Obviously, patient education is of crucial importance. No one, male or female, should receive a prescription for thalidomide without thorough counseling about the likelihood of birth defects if a fetus is exposed to thalidomide.

Written information about thalidomide should be provided in appropriate languages, and it should be written at a level that is understood by people who can't read well. In addition, we strongly urge the FDA to require the manufacturer to demonstrate that its written materials can be understood by a broad variety of patients.

We also urge the FDA to concentrate on

physician education. While there are probably few physicians unaware of the birth defects caused by thalidomide, there are, unfortunately, many physicians who do an inadequate job of counseling patients about the effects of drugs.

The manufacturer of thalidomide should be required to provide physician education materials similar to those used in the Accutane pregnancy prevention program. We observed the presentation earlier this morning, and it seems that a lot of thought has been given to that area. I would just add that we would be very excited to see, in what might be one of the few times any of us ever got to see it, some evidence that physician education materials are effective at their job and change the knowledge of physicians. But we can certainly see, as I'm sure the committee did, the protections that are built into that system.

But particularly, in addition to the educational aspects of the fetal protection programs, we would also like to address what we consider the behavioral aspects, or the need of women to use contraception. Throughout the morning, we have heard quite a variety of comments on that topic. We've heard the most extreme measures that were taken out in the Public Health Service IND, requiring premenopausal women to either be sterilized

or to be hospitalized. That was effective, but it's certainly not what we or, we hope, you would recommend.

We have also heard that challenged by a member of the committee. Thank goodness.

We have also heard a recommendation that women use two methods of contraception. We also heard, early in the morning from a representative of the pediatricians' groups, a belief that certain women, especially women who are HIV positive and have other problems in their lives, are likely to be non-compliant. We are concerned that in the well-meaning efforts and concerns that all of us have of protecting fetuses and preventing hopefully all, or at least as many as possible, fetal exposures that could happen if thalidomide were approved, that this attention is going to swing too far and is going to create a climate where women are considered the enemies of their fetuses.

Women do not want to have children with birth defects. They do not want to take drugs that will cause birth defects, and get pregnant and expose a baby to that. Not everyone can act on their wants as simply as I have described them, but I think we have to keep coming back to that, and remember that what our efforts should be concentrated on are identifying the women who are most at risk and supporting them to act responsibly, to protect themselves and, if possible, a fetus against that risk.

We recommend that all patients be counseled thoroughly about the risks associated with thalidomide and the importance of never sharing the drug. Physicians treating female patients must have a sensitive and respectful discussion with each woman about whether there's any chance she will have intercourse while taking thalidomide. Women who describe themselves as celibate or only having sex with other women, or non-vaginal sex with men, should not be forced to use contraception they do not need.

However, we do agree with the recommendation made by others that every woman, regardless of her description of her sexual activity, be prescribed emergency contraceptive pills just in case intercourse occurs against the woman's will or in a completely unexpected manner.

The situation of young women whose health care is being managed by a parent is especially sensitive. Many young people will not honestly admit their sexual activity in front of a parent, and may not be truthful with a care provider as a result. Clinicians must have a private conversation with a young woman who they are considering prescribing thalidomide for. Clinicians also need to counsel parents that contraceptive use is an important component of the safe use of thalidomide.

But in what will probably be the most common

case of women of reproductive age, women who admit to their physicians that they do anticipate having vaginal intercourse while they are taking thalidomide, we believe that counseling should encourage the use of the most effective contraceptive that is acceptable to that woman. And we believe that, in most cases, that will be the most effective contraception based on our experience with women that they, like all of us, want to prevent preventable birth defects.

Clinicians have an extra responsibility here, though, to assure that women, who have been thoroughly counseled have made a decision about what contraception to use, are able to act on that decision. We understand Celgene is willing to make referrals to doctors who are competent at counseling on contraception, and that is an important step.

But what about the woman whose insurance, like so many private insurance, doesn't cover contraception, and other women for whom contraception poses a financial hardship?

Clinicians are going to need to expand their role as both healers and educators into a little bit of social work here, to make sure that every woman who makes the right decision is able to act on that right decision.

In conclusion, we would just like to say that

obviously, we're all aware that thalidomide may have an array of therapeutic uses. It's important for physicians to understand the possible ramifications of prescribing thalidomide, and it's also equally important for women to understand the risks. Given that understanding, we believe women will make good choices for themselves. And we believe it's not appropriate for the FDA or for medical authorities to go too far in making that choice for women and mandating the type of contraception that's used, as has been suggested in some other discussions about thalidomide.

Thank you.

DR. McGUIRE: Thank you very much, Ms. Pearson. I think you have described the dilemma very well. And, by the way, the committee does hope to do the right thing. It's just that we have to figure out what the right thing is.

MS. PEARSON: That's right. That is why we said it was actually harder this time around than in 1961.

DR. McGUIRE: We are going to hear from the American Behcet's Disease Association, from Ms. Vicki Walton.

MS. WALTON: Good afternoon, ladies and gentlemen. First, I would like to thank you for affording me this opportunity to speak with you today.

My name is Vicki Walton, and I am representing

the American Behcet's Disease Association. I come to you from Kemmerer, Wyoming, to ask you to please approve thalidomide. In my testimony, I will include a letter from my physician, as well as a letter from the person who has been my primary caregiver, my mother.

In 1980, at the age of 12, I was diagnosed with Behcet's disease, a devastating autoimmune disease, which proceeds over a long period of years in a series of remissions, lack of disease activity, and exacerbations, periods of disease activity. Symptoms can last for days or weeks or it can continue on for months and even years.

This enigmatic disease is a complex, multi-system disorder of mucocutaneous, ocular, neurological, intestinal, articular, urogenital, pulmonary, and other symptoms. Eye, vascular, and brain involvement are the more serious manifestations, which lead to blindness, blood clots in major veins and arteries and, at times, even death. Chronic mouth and/or genital ulcers, joint and muscle pain, as well as fatigue, are the most prevalent symptoms.

The manifestations of this disease may appear independently, such as ulcerative colitis, or all together, in a general flare. I have had nearly every symptom of this disease over the course of 17 years.

Treatment from Behcet's disease remains

primarily anti-inflammatory and immunosuppressant. I have used ever traditional therapy for Behcet's, including prednisone, Decadron, colcincine, chlorambucil, Imuran, and cytoxan. When one medication is no longer effective, my doctors would move on to another.

And I would like to add that all of these medications pose a threat to an unborn fetus.

The course of my disease has been a progression into what I refer to as a living hell. By 1991, I spent more time in the hospital than at home -- 350 days to be exact. I was 100 percent disabled. I relied on a wheelchair for mobility; however, I was basically bedridden.

My prognosis was not good. No traditional therapy helped. Then, in June 1991, in an edition of the American Behcet's Association newsletter, I found a glimmer of hope, an article about thalidomide. Initially, none of my physicians would prescribe it for me, because I was of childbearing years. Finally, my hometown family practitioner stepped forward. He jumped through all the necessary hoops, got an IND number, started me on birth control pills, and had a baseline nerve conductor study.

I began taking thalidomide in December of 1992. Each year, I have an EMG study. And I am happy to report that I have never experienced any harmful side effects from

thalidomide. Every 3 months I risk the chance of developing an ulceration from a needle stick to get the Depo Provera shot.

Thalidomide has been a miracle drug for me. Thanks to thalidomide, I am out of my wheelchair. It now serves as a spare chair in my computer room, and I serve on the Kemmerer City Council.

I would like to close with the letters from my mother and my doctor, and a final plea. Please remember that in all of this debate to do a greater good, that people like myself are caught in the cross-fire.

The first letter from my mother:

The decision to legalize thalidomide is, I am sure, a difficult one to consider. I am certain that you have received strong opposition to it. I respect your position as you ponder this matter, and I ask you to respect my position as a mother and caregiver to listen to this with an open mind.

I can only imagine the pain involved with being a parent of a victim of a birth defect caused by thalidomide. It must be horrendous. I do, however, know the pain involved with watching my beautiful child suffer through insurmountable pain, surgical procedures and to become, at one point, completely debilitated, wheelchair-bound, and eventually bedridden.

For two years, I was Vicki's primary caregiver as she laid in bed, agonizing in pain. She was septic over 18 times, and withered away to near death until the miracle of thalidomide was introduced into our lives. Within 10 months, Vicki was out of bed and out of her wheelchair, taking care of herself. Most importantly, she was able to enjoy the pleasures of being alive.

Vicki has made a remarkable recovery with her disease. She is by no means cured. She still has periods of remissions and exacerbations; however, she can now lead a full, productive life. She is currently serving her third year of a four-year term on the Kemmerer City Council, and dedicates much of her time to the youth of our community.

I know that thalidomide has caused a great deal of pain and suffering to those who have endured the worst side effects of this drug -- the birth defects. We must remember, however, that when it caused these tragedies, it was given specifically to pregnant women.

Research has proven that thalidomide holds great value for several types of diseases, my daughter's included. Many lives have been improved, enriched and possibly even saved by this drug. I know that ours has.

I would encourage you to let the positive outweigh the negative in making your decision. I implore

you to make this medication accessible to all who will benefit from it, not just one select group.

Education is by far the most important factor in administering this medication. We know the tragic results when a pregnant mother takes this drug. Common sense and self-responsibility go hand in hand with this medication, as well as every other known to man.

My prayers and thoughts are with you, along with my request to be realistic and allow this drug to become available by prescription to everyone, including my daughter, so that it may improve the quality of their lives.

Respectfully yours, Georgia Walton.

And I will conclude with a short letter from my physician, Dr. Craig Talbot, who is also the Chief of Staff at South Lincoln Medical Center.

Dears Sirs and Ma'am, I am currently treating two patients with Behcet's disease with thalidomide. Both of these women were placed on thalidomide because the other regimens available for this disease were not effective.

It was tedious and difficult for me, a practitioner in a small town, to comply with the same requirements that a pharmaceutical house complies with when they are developing a new drug. I have no way to support the costs involved. In fact, in order to treat these

patients, I am in violation of the IND guidelines, which state there will be no cost incurred by the participants in this study. I am not doing research; I am simply trying to help my patients, and am providing thalidomide to them at my cost, without any markup to cover the cost of handling, et cetera.

I would suggest that the FDA develop a set of rules for physicians who are simply trying to help their patients, who have nasty diseases for which no other regimens are available.

Thank you.

DR. McGUIRE: Thank you, Ms. Walton, for giving us a very personal account of your success.

The spokeswoman for the People with AIDS Health Group has generously acknowledged that most of what she wanted to say has already been said, and so we will go right ahead to the agency's view of this issue. And Dr. Wilkin will be the first presenter.

Ms. Cooper, thanks for your time.

DR. WILKIN: Well, we've heard multiple times now thalidomide has been to the agency once before. And of course, if you came to our November last year meeting of the committee, Dr. Kelsey gave a fine overview of the events of that time. And because she was still looking into the neuropathy issue at the time, when it became

evident that there were many babies being born with birth-related injuries, thalidomide injuries, that that is what ultimately led to thalidomide being withdrawn and not approved at that time.

So here we are, 40 years later, looking at thalidomide and rethinking what we might do.

If you look in any standard pharmacology textbook on drugs, and you look up thalidomide, you will be struck by how much larger the section is on history than it often is for many of the other drugs. In fact, in some accounts, there is more written under the history section than there is on the other sections. So, it is a molecule with a history, and we do not ordinarily have molecules come to the agency in new drug applications that have such a legacy that we need to think through.

But I would ask that you look back on what has happened and consider those aspects of thalidomide that are truly properties of the molecule versus those properties which were of the human systems at that time -- the drug development systems and the drug regulatory systems around the world.

So, what I did in preparing my welcome back, literally, for the committee to think about thalidomide, since you considered it last November, is I went over the discussions at that meeting, and I came up with a list of

what I thought were some of the key elements that seemed to be troubling some of the members of the committee. And I thought I would go over those, and we could think about some of the deliberations that the committee has had in the past.

Basically, they are the importance of the historical tragedy, that it is a potent teratogen, the concern that ENL is rarely life threatening, and yet we are considering a drug of this magnitude, that other drugs might be effective for ENL, and then of course, the concern about the potential for off-label use.

Again, for the first one, I would urge you to think of the tragedy, the extremely profound tragedy, that came from thalidomide as a property, in large part, of the human systems at the time -- the regulatory review boards in the different countries that approved it on very little data and also the type of drug development that actually was in vogue at the time. That was the standard of that day.

We have different standards today, and I think we know a lot more about this particular drug today.

So, separate history from what is really a property of the molecule. We have other teratogens that have been approved after thalidomide came in the early 1960s, and we do not have the tragedies that have been

reported for thalidomide.

I'll just point out that the dermatologists who are here, many of them have probably used most of the drugs on this list. Dermatologists frequently will use teratogens in their practice. And if we consider these and consider some of the regulatory recommendations that this committee has made to the agency in the past, and ultimately how these drugs have been approved, I think we can answer some of the concerns that were mentioned previously regarding thalidomide.

All of these are potent teratogens. And I think the committee would agree that they find acitretin, etretinate and isotretinoin -- there have been strong arguments from the committee to have these approved.

ENL is really life-threatening. Acitretin and etretinate are for psoriasis and really not many of those patients with psoriasis for whom they would be receiving these retinoids would there psoriasis be life-threatening. It could be severe, but it might not be life-threatening.

With isotretinoin, that is for cystic acne. Cystic acne can ruin lives, but cystic acne does not end lives. It is not life-threatening in that sense.

Then the potential for off-label use. I think in dermatology we see reports virtually every month in the journals about retinoids being employed in disordered of

keratinization. There are many, many dermatoses, maybe 3,000 separate dermatoses. We know that not all of them are always going to have drugs approved for those particular indications. And so there is going to be off-label use. So, that happens with the drugs that we have listed here.

So, again, the list of things that I took away from the November of last year advisory committee as being some of the key elements that were worrying some members of the committee, and I think appropriately so. I think these are issues that really need to be discussed and to be thought about. But, also remember, the decisions that have been recommended to the FDA by this committee in the past.

So, I would ask the committee to think deeply about the questions that are in the package. That is the process and, in a manner, to search for the potential therapeutic good in thalidomide. This is good. Not just is there efficacy, but this is good in the overall risk/benefit relationship.

I would add at this point, just as a additional comment to what Dr. Weintraub said this morning, that the FDA does not only permit diversity of opinion, but I think actually fosters it -- encourages reviewers to think through and come to their own point of view after they've looked at the data.

There are, in your packets, reviews by Drs. Vaughan, O'Connell, and myself, and the committee members also received this morning two additional reviews from Dr. O'Connell. And I would just say that they are up-to-the-minute, and I checked with both of the reviewers, and they feel comfortable with everything that they have written to date. So, if you want to look at that this evening, that would be some more information for you.

One final caveat in thinking through thalidomide for erythema nodosum leprosum. Erythema nodosum leprosum is an ambiguous medical term.

If you look in the textbooks and papers, it has been used to describe the nodular lesions of this particular reaction. It has also been used as an epithet for the entire systemic reaction, including fever and the nodules. So, I would ask that when folks are up here and they are talking about erythema nodosum leprosum, that you think in your mind what exactly do they mean. Are they talking about skin lesions now or are they talking about the whole syndrome?

I think that would be one question that we might ask the sponsor. They presented a new indication. And in your indication it said, erythema nodosum leprosum. I guess you could define that as, you know, the whole systemic syndrome -- or whether you are defining it as the

cutaneous lesions of erythema nodosum leprosum.

Thank you.

DR. McGUIRE: Yes. This is Dr. Kilpatrick.

DR. KILPATRICK: Earlier this morning, there was some reference to thalidomide not having a low-dose threshold for teratogenic effect. I have forgotten who made that or whether it was in one of the earlier written presentations. But my specific question to you Jon is whether anything is known about these teratogens that you presented, in terms of low-dose threshold.

DR. WILKIN: Yes, for the retinoids, we do not know of a systemic, for example, plasma concentration below which they would not be teratogenic. That is not to say they are teratogenic at really low levels; we just do not know what that level might be.

DR. McGUIRE: Yes, a question?

DR. MOORE: Hi, Dr. Wilkin, I have a question.

DR. McGUIRE: This is Dr. Moore.

DR. MOORE: For that list of teratogens that you put up there -- and you were talking about this committee, or FDA's actions in the past, in considering those drugs and they are now on the market -- how many of those drugs were known to be teratogenic in humans, proven to be teratogenic in humans, at the time that they were being considered for approval?

DR. WILKIN: Okay, the ones that were FDA approved for dermatologic indications, where I think dermatologists used them most, would be the top three on the -- it would be the right-handed panel. It's the three systemic retinoids. For all of those, it was known that they were teratogenic before they were approved.

DR. MOORE: In humans?

DR. WILKIN: In humans. Isotretinoin, etretinate, acitretin.

DR. McGUIRE: There will be a period for discussion of the agency presentation. I would like to go next to Dr. Barbara Hill, who will discuss nonclinical toxicology.

DR. HILL: As was mentioned, the purpose of my presentation this afternoon is to focus on the nonclinical pharmacology/toxicology data that was submitted for the NDA package, looking at thalidomide for the ENL indication.

This next slide is an outline of what will be discussed, and it provides an overview of the information that was submitted in this package for the nonclinical studies. I will first go over the absorption, distribution, metabolism, elimination studies, the pharmacokinetic results, then go over multi-dose toxicity and chronic toxicity studies. I'll next discuss the mutagenicity results, and then go over the studies that

were proposed for a phase IV commitment, which are the reproductive toxicity and the carcinogenicity studies.

This slide gives a list of the pharmacokinetic studies that were submitted for the NDA. And there were studies performed in mice, rats and dogs.

The mouse studies consisted of a single-dose; a 14-day repeat dose, where samples were taken on day 1 and 8; and a 90-day repeat dose study, where samples were taken on day 1 and 90.

The rat studies consisted also of a single-dose, a 14-day study and a 90-day study.

The dog study consisted of a 7-day repeat dose study, with samples taken on day 1 and 7.

The findings that were seen with these studies are that the thalidomide absorption was dose proportional at low thalidomide dose levels and became nonlinear at higher dose levels. And this is probably due to the inherent low water solubility of the product. The bottom line is that absorption becomes saturated with increased dose. So, once you get above a certain does, there is no increase in systemic absorption of the drug.

This next slide lists the multi-dose toxicity studies conducted in mice, which consisted of a 14-day mouse study and a 13-week mouse study. The 13-week study serves as a dose-ranging finding study for the

carcinogenicity assay. The findings from these studies showed a treatment-related formation of discolored urine -- in this case it was a red/pinkish color. The sponsor also conducted studies to show that that was not due to the formation of blood in the urine. It was probably due to the formation of a chromaphore in the urine.

There was also a dose-dependent severity of centrilobular hepatocellular hypertrophy, with corresponding increased liver weight. I would like to comment that this may be a species-related effect, because it has been shown in mice that with high dosages of xenobiotics, you see a similar type effect.

But what was most interesting is that, in the 14-day study, you saw the formation of cataracts, and in the 90-day study, you saw the formation of corneal crystals. The exact importance of these studies is not known at this time.

This next slide shows some multi-dose studies performed in rats, which also consisted of a 14-day repeat dose study and a 13-week repeat dose study that will also serve as a dose-ranging finding study for the carcinogenicity assay. In the findings from these studies, they saw a dose-dependent decrease in body weight in male rats, a dose-dependent increase in platelet count. Also there was a mild leukopenia.

There was a treatment-related effect in the thyroid function. A treatment-related decrease in the thymus weight. And the sponsor, in a 13-week study, was hoping to be able to use this to look at potential peripheral neuropathy. They did a behavioral test, and they also examined the sural nerves.

But what was seen in this study is a general degradation of sural nerves in male rates from all groups, including the control group. So, this animal model will not serve as a good model for that purpose.

In the dogs, they did a 28-day repeat dose study. And the only findings that were seen in this study was a dose-dependent formation of discolored urine. In this case it was a blue/green color, as opposed to the mouse, which was red/pink. It was possibly due to a spontaneous hydrolysis product which serves as a chromaphore, and there is evidence in the literature to suggest that some of the spontaneous hydrolysis products could act as chromaphores.

The chronic toxicity study that was performed in support of this NDA was a 1-year dog study. At the time of the NDA submission, the 6-month interim report was submitted. And the findings from this 6-month report was a dose-dependent incidence of discolored urine similar to what was seen in the 28-day study. There was also a

treatment-related enlargement of mammary tissue, a dose-dependent increase in discoloration of the cranial bones. And there was a slight axonal swelling, with loss of neurofilaments in two high-dose male dogs.

The 1-year final audited report will be submitted as a safety update, and the results from that will become important to determine if this axonal swelling is due to treatment-related effect or, as the contract lab suggests, is related to the histopathological processing of the samples.

The sponsor conducted a full standard battery of tests to examine the mutagenicity of thalidomide. They tested thalidomide in the Ames test, in the AS52/XPRT mammalian cell forward gene mutation assay, and also in the in vivo micronucleus test. This will look at the effects on the mouse bone marrow of anthropodiac cells.

The findings from these three battery of tests demonstrated that thalidomide was not mutagenic in any of these assay systems. But it is important to note that there is some concern over, at least for the in vitro tests, concerning the stability of thalidomide at neutral pH in the two in vitro assays due to what has already been discussed -- a rapid rate of hydrolysis at a neutral pH.

The next two slides give a brief listing of the studies that were agreed to as a phase IV commitment. This

first slide shows the reproductive toxicity tests that will be conducted. The sponsor will conduct a dose-range finding study in rabbits. The results of this will serve to establish the doses for the next two studies -- the first being a segment 1 study in rabbits. The purpose of this will be to look at the potential for thalidomide transfer via semen.

They will also conduct a segment 3 study in rabbits. And the importance of this study is to examine the effects of thalidomide during late pregnancy -- for example, during the third trimester -- as well as to establish the phocomelia effects of thalidomide during early pregnancy. But the effects in late pregnancy are not well established.

And this next slide shows that, as a phase IV commitment, the sponsor has agreed to conduct two 2-year carcinogenicity studies in mice and rats.

And this last slide just gives a summary of the information that we hope to learn from the nine clinical studies that were submitted in this package, and agreed upon in a phase IV commitment. And that is to achieve a better understanding of the absorption, distribution, metabolism, and elimination profile for thalidomide, to characterize the potential toxicities after long-term use of thalidomide, to characterize the mutagenic and

carcinogenic potential for thalidomide, and, in addition, to expand the knowledge concerning the reproductive toxicity potential for thalidomide, and hopefully to be able to characterize the peripheral neuropathy for thalidomide.

Thank you for your attention.

DR. McGUIRE: Unless there are burning questions, I'd like to go ahead with the next speaker, who is Dennis Bashaw, who will address clinical pharmacology.

DR. BASHAW: Actually, we won't be addressing clinical pharmacology at all with regard to thalidomide pharmacokinetics, primarily because the clinical pharmacology, when you look at the definition of it, certainly encompasses biopharmaceutics also, which is going to be the primary focus of our talk, but it really also encompasses association of concentration effect relationships, or biological understanding of the mechanisms of action.

Clearly, with thalidomide, there has been a lot published and there has been a number of articles published about proposed mechanisms, both of its activity in different autoimmune disorders and also its activity as teratogen.

The popular theory that has been published very extensively right now is the role of TNF-alpha. However,

if you look at the literature critically, you can find articles that say TNF-alpha goes up, it goes down, and it is basically unchanged with thalidomide treatment. There has also been some recent work, basically stating that, well, there is modulation of TNF-alpha, but at super-pharmacologic doses that are really not reasonable in man. So, the role of TNF-alpha in thalidomide, and what we would consider true clinical pharmacology is really still unknown.

And that is really not anything against the approvability or non-approvability of thalidomide, it just needs to be brought out that true underlying mechanisms really are not really very well understood. But, then again, they aren't for a lot of drugs either.

Instead, today, we are going to talk about the pharmacokinetics of thalidomide from Celgene's dosage form. Originally, the schedule that I was given had me coming before Dr. Colburn, and I found out this morning it was arranged a little bit differently, so some parts of my talk will need to be modified a little bit to reflect the information he presented.

Just yesterday morning, we were given advanced copies, or advanced information, that he was going to present. We were unaware that some of the results he presented actually had come in. So, some of the data

which, on my overheads, are listed as things planned or things ongoing, actually have been completed. Yet, we have not received them for review in the FDA. And I will make those points when we come to them.

Basically, just as a review of the material, which you have already received in my review in your package, these are the three completed studies that were reviewed and are contained in my review:

A single-dose bioequivalency study, looking at the to-be-marketed versus a clinically studied formulation by Celgene. This also included the Tortuga formulations as a third arm in that trial.

A dose-proportionality study in healthy volunteers over a range of 50 milligrams to 400 milligrams.

And a metabolism disposition study in patients in leprosy. This was a study which, again, Dr. Colburn described earlier, where we were looking at the parent drug, plus the most likely, we thought, metabolites at that time in the plasma and in the urine.

This you saw earlier -- a text form here. At least we complement each other. He presented the text portion of it; I have got the graph here for you, which has been excerpted from my review. You can clearly see that when one compares the two different formulations of Celgene's product that they are, statistically and they are

from a regulatory perspective, bioequivalent. It does show, however, that there is a significant difference in the bioavailability and the disposition pattern between Celgene's product and the Tortuga formulation.

I think this has some implications later on, once you start to go into your deliberations, about trying to extrapolate some of this data from different formulations and different databases as to what the exposure truly is. Now, admittedly, this is single-dose data, and one would expect with multiple dosing that the differences might come together a little bit. Again, there was some allusions to some simulation work this morning that showed that in fact the peaks did become very similar with multiple dosing with the Tortuga product, based on simulation work, not on real data.

I think that is interesting, and I would like to see the simulation work before I really could pronounce whether or not that is really the case. My concern here, as you can see very easily, is that you have very different elimination curves, very different disposition curves. And this was referred to earlier as the flip-flop model in pharmacokinetics.

Basically, you normally assume that once you have entered -- after a couple of hours, absorption has ceased and you have a true elimination rate, which is what

you normally see. Here, instead, it is very obvious that you have continued absorption, continuing on at later time points, which is causing an elevation of plasma levels and also a calculation of a longer plasma half-life.

We are hoping, with some future research, to be able to get a better handle upon the true bioavailability and disposition of thalidomide from the dosage form. But I think it is important just to keep these differences in perspective and to remember them as you go on to your deliberations.

Here we have the dose proportionality data, again, referred to earlier. I think you can see pretty nicely that from 50 milligrams, 200 milligrams and 400 milligrams, you do have dose proportionality. This was done in healthy volunteers, using a range of doses. Really, you are still seeing the same pattern of half-lives there that is very consistent. The half-life here is about 10 to 12 hours, I believe -- I'm sorry -- about 7 hours.

Going to the next overhead, which, if you will allow me to orient you to this, we are looking here at the degree of proportionality, trying to look at it by a parameter basis. The green line and the blue lines are the dose-normalized area under the curve, both 0 to tau and 0 to infinity. Ideally, you should have a line that has a slope equivalent or not very different from 0. In fact,

what you're seeing there is really not that different, and statistically, you would say they are dose proportional.

Clearly, the red line, which represents Cmax, you do see is dropping off with the higher dose. What is really happening there, I think, is in this particular study, with a 50 milligram dosage form, you are putting 8 capsules into the GI tract of a drug that has very poor solubility. It is just that you had a very large mass of power that was not being absorbed very rapidly.

Eventually we know, from the area under the curve, it does get absorbed. It just does not get absorbed rapidly enough to show a proportionate increase in plasma levels.

Again, I think the message here is that if you are thinking of larger doses, there is going to be some limitation to what peak levels you can achieve. Again, that all sort of goes back to the question of what is important. Peak levels or area or sustained levels? Again, that is a question we really do not have a good handle on right now.

This was a study we tried to look at metabolism of thalidomide. We did a study in patients with leprosy, 6 patients, and we saw some interesting results. The red line that you see there is a subset of all the patients. The blue line, which shows a much higher plasma

concentration -- of course, this is a mean line -- is somewhat higher.

In this study, there were 6 subjects, and 2 of them were very different from the other ones. There was really no real reason why. There is some suggestion that they had more severe disease, but, then again, they were all receiving the same dose, and there was not a real good understanding as to why they did have these higher levels.

When they were taken out, clearly, when you look at the comparison back to the old data from the previous study, which is the green line, the red and green lines do show some similarity, even with the other patients. When one looks at the elimination rate, one sees that they are very similar across all three groups.

What could this possibly be is hard to say. Unfortunately, doing a very small study with 6 subjects, it is hard to make hard and firm conclusions. There is also the complicating factor that these 6 subjects were on a total of 47 different medications, when you go through their patient records. So, whether or not you are seeing drug-drug interactions -- maybe not of the metabolic type, but maybe in absorption, maybe there is some interaction happening in the GI tract that is either facilitating absorption or slowing it down. That's a possibility that we really cannot give a firm answer to right now.

But I think what the message to say here is, is that, in general, the pharmacokinetics from people with leprosy versus normal volunteers are not that different. There is this increase in peak, which we really can't explain, but with the small number of subjects in this trial, it is very hard to say that that is a very hard and fast rule.

One was hoping -- and I understand now the study has been completed -- we would get some more data from the steady state study. Some of that information will help us get a better idea as to what kinds of accumulation kinetics we are going to see at steady state dosing. But, again, I have not yet had a chance to review that information.

Not to dwell too much on this graph -- there is a lot of text up here -- basically, again, it goes over the fact that there was a drug metabolism study done, that it did look at the most common P450 isoenzymes, 1A2, 3A4, 2D6, the ones that participate in a majority of all human drug metabolism. They use a wide range of concentrations, pH values, and really did a very good study, in terms of looking at and trying to find metabolic interactions. I think it was a very well-done study.

In effect, what you found was exactly what was reported earlier, that thalidomide was not metabolized to

any significant extent by any of the common P450 isoforms, and they used concentrations up to 40 times the peak plasma concentrations seen with their highest dose. So, as I said, it is a pretty good test, we think. And even increasing the amount of enzyme, making it more than normal, still did not cause any additional metabolism or any change in the formation of metabolites.

From the other standpoint, you always like to know, not only is the drug metabolized by the enzymes, but what effect does it have on metabolizing enzymes themselves. By repeating the study with control samples with known substrates, it was found that thalidomide did not participate in, did not inhibit, did not enhance any drug metabolizing enzymes. So, in fact, it really basically goes back to the conclusion that thalidomide is not really a metabolic player in the P450 metabolism scheme.

Again, some of these studies -- and I will go through them very quickly for you -- have already been discussed and have already been reported out.

The multiple-dose steady state study, which was part of a clinical trial, some of those results have come in. We have not yet had a chance to review them. Dr. Colburn, again, went over them this morning.

The food effect study has already been discussed.

Special populations. Depending on what the committee does, we can develop some kind of language for that. Trying to do special population studies in a special population already is especially very difficult. And with the in vitro metabolism data, I think we can probably address the hepatic without too much difficulty.

The renal is sort of a question mark, because we really don't understand what is thalidomide broken down into and where does it go. So, renal may still be an issue we want to think about and give some thought to.

Drug interaction studies. Again, the oral contraceptives study has been done and been reported out. Again, we originally discussed at the previous advisory committee some need for some other studies, possibly with dapsone, possibly with rifampin, and other agents likely to be given. I think now that we have the P450 information, we may want to revisit that issue. If the committee has any ideas or the sponsor themselves, that could be revisited -- the need for those studies -- because we clearly have this information, which really seems pretty solid.

One thing I would like to apprise the committee of is one of the original problems we had working with this product was that thalidomide is just so insoluble as a chemical substance. Its solubility in water is .06

milligrams per ml. If we were going to give a patient a solution dose form of it, it would basically take about a gallon of water to get the dose in, which really is not very realistic for pharmacokinetic studies. Or even to get the patients in and have them drink this in a short period of time is not very realistic, especially for a drug that undergoes hydrolysis.

Since then, we have been doing some research with the FDA laboratories, and some solvents that are feasible have been developed. The sponsor has committed to, and we have had discussions about, a protocol. We have sent comments back and forth. We are working with them on developing a protocol where this will be looked at.

The advantage of this study is that by using a solution dosage form, in addition to their oral capsule -- I won't go into the process, but through a process of deconvolution of the plasma level time curve, we will be able to look at the way that the thalidomide is absorbed -- a surrogate for bioavailability; it is not really bioavailability -- but we will get a better assessment of the rate and this issue of the flip-flop model, where we have this continued absorption and continuing laid out, we will be able to assess that degree from the study.

So, that's really going to be a very good study and very useful from a pharmacokinetic standpoint. But

that is a planned study. We are still working with the sponsor on that. And really, we are looking forward to that one.

So, summing up, I guess the question is with thalidomide: What do we know and what don't we know about the pharmacokinetics? And really, I think, some of these things should be considered as part of your deliberations as to how you make and how you weight data, and what you would like to see done in the future. If you have any other ideas that you would like to suggest both to us and the sponsor, or questions, we have some issues here that we would like to have you consider and go over with you.

Starting off on the plus side of the ledger, we certainly know that Celgene's product is bioequivalent to what was used, both clinically studied and what they propose for marketing. We know that we have dose proportionality in exposure, but not in peak levels at single dose. Whether or not that follows through to steady state or that comes together is not known. We are, again, hoping some of that steady state data, which they have collected but we have not yet seen, may help us answer that information. And also we are very interested in working with them on the simulation work also, and trying to see where it is going.

We think that it has similar pharmacokinetic

characteristics in Hansen's disease patients. Yes, there were 2 patients who were aberrant, but in terms of their distribution and their elimination -- and when you look at those aspects of the curves -- they were very similar. It seems like what you were seeing is there may have been absorption change. And I think that may have been due to some other concomitant medications they were on.

It is speculative, but it was a limited study, and I think that is about all you can really say. It's not a very solid study, because of its numbers.

It is bio-inequivalent to the Tortuga form at single dose. Again, at steady state, at this point, we really can't say is it bioequivalent or not. I think the word this morning was very well chosen -- they said they were similar levels -- but what is similar? We tend to, in the agency, from a biopharmaceutics point of view, look at things from bioequivalency, using bioequivalency testing, which is a high standard, but it does allow, and has allowed, historically, for extrapolation from one formulation to another to another, applying a standard across all products.

We don't believe it's very highly metabolized or participating in P450 mediated metabolism. It does undergo hydrolysis. In your package, in the review, I attached an article to my review which talked about, a

little bit, all the different potential hydrolysis products and where they could go. And I think that is really the unknown right now if you were to ask what happens to thalidomide. Certainly, it gets broken down -- not by metabolic means, but by hydrolysis. What happens to those products we don't really know.

We looked, trying to use a technique we thought was adequate, but it really didn't have the resolution we needed. Whether or not this needs to be pursued, I think we would like to get some feedback from the committee on this and what techniques we should be thinking of.

Finally, what we don't know. Again, I will modify this again from the presentation this morning. We don't know the metabolic fate in humans. We don't. I've already discussed that.

The relative bioavailability from the capsule dosage form. We don't know that, but again, there are steps being taken to address that and we have, I think, a good plan underway to look into that issue. So, that is going to be taken care of very quickly.

The importance of AUC or Cmax relative to efficacy or safety is an unknown. There's not enough information, we feel, from the pharmacokinetic database or even from the published literature that makes us comfortable one way or another. Again, we would be

interested in any input or insight people would like to offer in that area.

Mechanism of action. Again, TNF-alpha has been proposed, but the literature is very unclear there. Again, that is not really a plus or a minus. There are many drugs we don't know mechanisms of actions for, but we thought we would put it up there anyway.

Effect of meals. Certainly that study has been conducted and has been reported out. Once we receive it, we will review it. From the preliminary information presented this morning, it doesn't seem to really provide any real changes in bioavailability or absorption. I think there was some delay in time to peak, but that is not really unexpected for most drugs.

Effect of gender. We do have the results -- well, we do not have -- the results are coming in from the oral contraceptive study. And certainly that information will help us deal with that issue of gender-related pharmacokinetic changes.

Presence or absence of interaction with oral contraceptives. Well, we have the study now -- well, again, it's coming in -- with the Ortho Novums, and we will be able to assess the pharmacokinetic interaction. I don't mean to bring this up to start anything, but there is the issue of the pharmacodynamic interaction. And there have

been some discussions in the FDA about changing the way we do oral contraceptive studies. But what they did was the way we do them now.

I think, in the future, you may see some changes in that. And we may actually ask the committee to give some feedback on that at a future meeting. But the tests they did right now were certainly consistent with the state-of-the-art that we are doing now. But I just wanted to let you all know that that may be changing, and we may be asking this committee to give some feedback, because of its experience with retinoids and other agents.

We do want to talk just for a second about racemization. This is something I have always tried to bring up at every meeting, because it comes up again and again. There were some publications in the mid-1970s basically stating that the teratogenicity of thalidomide was due to one isomer, and that had we only given the other isomer, things would have been all right.

I just want to beat that to death somewhat. New studies have shown that there is in fact rapid isomerization/racemization in vivo in humans, such that if you were to give the one isomer, you would produce the other in vivo, so that there is no way to get around it if it was assigned to one particular isomer. If you gave the R, you'd get the S in vivo, and vice versa. So, that is

not really an issue.

There is, however, a modest issue, and it is from the literature and we are looking at it, regarding about is there -- there appears to be -- or at least there is a publication that suggests that there is a difference in the rate of formation or the rate of interconversion between the isomers, such that after a long period of time, you might see an altered ratio. A true racemate is 50/50.

There's some suggestion that, with steady state dosing over a long period of time, that the ratio might change from 50/50 to 70/30, which is interesting kinetically. From my standpoint, it's very interesting. I think we will follow up on that, with getting some samples in the steady state study, and looking to see if there is a ratio change. But, beyond that, I do not think it will enter into your discussions very much.

Pretty much, that's a synopsis of my review, where we are at now and what our state-of-the-art thinking is with thalidomide pharmacokinetics.

And, next speaker?

DR. McGUIRE: Dr. Bashaw, thanks very much.

Dr. Wilkin, are we going to hear from the primary or the secondary reviewer in your division?

DR. WILKIN: No.

DR. McGUIRE: Dr. Michael Weintraub will give

an overview on which to base a regulatory action.

DR. WOODCOCK: Dr. McGuire?

DR. McGUIRE: Yes.

DR. WOODCOCK: There certainly will be an opportunity to ask the reviewers questions about their reviews?

DR. McGUIRE: Yes. I wondered if there was going to be a formal presentation by either reviewer. Thank you.

DR. WEINTRAUB: Good afternoon.

I am going to talk a little bit about the L.A. data. Now, these data were gathered and analyzed by the Food and Drug Administration, and the graphs I am going to show you were presented to me by Dr. Gao and Dr. Srinivasan, and also Dr. Steve Thomas.

Some aspects of these data are not the whole syndrome of ENL. I did want to make that clear, because Jon Wilkin had made the distinction -- what was the whole syndrome and what was the cutaneous syndrome. So, we have focused on the cutaneous syndrome in this particular case, because we really don't have enough data on the whole syndrome, and it's a little too difficult to discuss with you.

Now, basically, what we are doing here is looking at records kept for clinic purposes. These were

not necessarily records kept for research purposes. Yet, they were very carefully kept, and I think can offer us some very important insights. We're going to look at the challenge and de-challenge and re-challenge of the medication in the syndrome of cutaneous ENL.

Now, the first thing I did when I looked at these charts, which was much different than the primary and secondary reviewers, I separated them out and looked first at a subset of patients who had only received thalidomide. I felt that this was going to be one of the cleaner groups. This may not be perfectly clean, but, in any case, they only received thalidomide as their treatment for ENL.

When I did that, I separated out 46 of them. The way they broke down were 24 of the 46, or about 52 percent, were positive; 15 were not wholly positive, but were more negative -- or at least I called them negative; and 7, we did not have enough data to really discuss the 7.

Now, looking at the first one, let me tell you what we have here. It is never easy, I understand, to see these slides. I wonder if you could move it up a little bit, Mary Jane. Thank you.

On this axis, we have skin lesions: new lesions, yes; new lesions, no data; new lesions, no -- not no data, but no answer; thalidomide on; thalidomide off; and the daily dose of thalidomide. Across the x axis, we

have the time in weeks, and this patient was on for nearly 900 weeks that we had some information.

But I show this first as an example of not having enough information to make an understanding. Here, although the patient was begun on thalidomide, we have no data. The patient was begun on thalidomide, we have no data. The patient was stopped on thalidomide, we have no data. And we only have very sketchy data as to the amount of the dose.

But, as I say, not to criticize these data, these are common in a clinic-type setting. Now, you can see I only have talked here about the cutaneous lesions.

Now, this next slide is over a 40-week period. And the x axis changes on all of these. And, here again, we have skin lesions, thalidomide on and off, and the dose. We have a little more data here; no data actually for this time point, so we don't know even where it was. We can make an assumption, that the patient was begun on thalidomide, but we have no way of knowing what was happening. All we have is some very sketchy information about the dose.

I wonder if we could have the lights down just a little bit, because you can actually see the colors. These are all colors. They are not as beautiful as Dr. Bashaw's colors, but they are relatively --

This is an example of a single challenge and de-challenge over a 50-week, or 1-year, period -- sort of, about 42 weeks. New lesions was yes. The patient was begun on thalidomide. Next time the patient was seen, which was about 2 weeks later, no new lesions. And that carried on.

Now, this particular time, there was no data collected, but, soon after, when drug was still being administered, no new lesions, no new lesions. Then, although the thalidomide was stopped at this point, no new lesions.

Now, what we can learn from these are some very interesting points. First of all, the 100-milligram dose was the initial dose. It dropped to 50 milligrams very rapidly -- probably in the first month or so -- and then continued 50 milligrams all this time, and then stopped. So, we can see this is a very clean, very clear, single demonstration.

The question comes up, however, what about multiple administrations?

The patient had new lesions, was begun on thalidomide and seen very quick. This is a 300-week axis, but the patients were seen very quickly. The dose was 200. This patient was kept on 200 for several weeks, with always no new lesions, and then the dose was lowered to 100. No

new lesions again. The dose was kept was lowered to 50. It went 200, 100, 50. And then the drug was stopped.

When next seen, the patient again had new lesions, after being off the drug for some time, and thalidomide was begun again. Unfortunately, because of the way the data are collected, we have to do some inferring here, but he was clearly off the drug before these new lesions appeared. When seen actually a good many weeks later, he was still on the drug. Lesions had disappeared, no new lesions, and he was continued on that all along.

You can see here that the dose was 200 initially, 100, 50, back to 100 when the lesions recurred, when there was recrudescence of his disease, kept on 100, and that is where our data collection ended.

This, too, is a multiple episode of challenge, de-challenge, re-challenge. This, again, is at week 0 of the 170 weeks on the x axis. This time the patient was seen when new lesions occurred. The drug thalidomide was begun. We do not have any data on new lesions here, but the drug was begun and kept on the same dose. Was seen here with no new lesions. Again, no new lesions, no new lesions. And the drug dropped from 200 milligrams initially to 100 milligrams. Kept on 100 milligrams up to here. Was taken off the drug.

Unfortunately, this was a so-called virtual

visit. We had definite information that the patient was off the medication, but no data was obtained, because it's a virtual visit, just one to show that there was no drug being administered at that time.

However, he returned, had new lesions. The drug was begun again. Then, out here, kept on the drug at 100 milligrams a day, and no new lesions.

Now, here again, we have evidence that the patient was off the drug for some time. We definitely know he was off the drug. Then, when he returned, new lesions had occurred, and when the drug was begun again at a dose of 100 milligrams, the new lesions disappeared.

These are the best examples one could say. A teacher of mine in medical school had discovered the Philadelphia chromosome, and one day in pathology class, he showed us a slide of the Philadelphia chromosome. He said, this is a typical example of the Philadelphia chromosome. Of course, I looked at 8,953 slides before I came upon this one slide which is typical. In any case, these are quite typical, believe me, of the various 24 positives.

Now, these are examples of the failures. It's a little hard to see. In this case, there were new lesions and although the patient was seen quite rapidly -- this is a 600-week x axis. The patient was seen twice here, very rapidly, and did not improve on thalidomide. So, there are

two dots there.

When seen next, 2 years later approximately, it was off drug, new lesions occurred, again was treated for the new lesions. Again, there was no response. He was taken off the drug, put back on the drug, and then there was a recrudescent lesion. And, as I said, this is a time when we are sure he was off the drug. It was begun again, and this time had some success.

However, we can't really interpret this success as cleanly a we could the other, because, despite the fact that he was on thalidomide, in both cases, there was a very delayed response, if any response, because we don't have any data showing a response, and I called this a failure.

The one thing we can get from the dosing information, 100 milligrams did not seem to help him. He was given 200 milligrams the following time and tapered to 100 milligrams, but again, may have been helped, or it may have just been the passage of time.

So, you can see that some of the recrudescences can occur on thalidomide itself. And here is one where the patient was off of thalidomide, no new lesions. Was put back on thalidomide. And it is, again, a little hard to tell about the timing, but it is possible that this first episode was treated with thalidomide, but it is unlikely. And here, was off the medication and on the medication, and

may have, again, had a response.

However, we have no information here about this patient being off the medication. And it may have been that he had continued on the medication at 100 milligrams a day and had a recrudescence of the disease while on thalidomide. It's possible.

Again, here, this appears to be a recrudescence on thalidomide. Here he was off thalidomide. We do not have good data, but there is a possibility of more disease.

Now, this next patient -- this is the first 300 weeks of his course -- was on therapy for a very long time. You can see, again, that there may have been a recrudescence while on thalidomide. However, this dot indicates that he was off thalidomide again, put back on, and had a decrease in his skin lesions.

So, you can see, this is a mixed case, but I decided that, in looking at it and investigating it, that in fact this was a negative case. You can make an argument, but it's what I took as a negative case.

Now, the issue of steroid sparing. There were 56 patients on a combination of steroids or clofazimine, and I decided not to look at the clofazimine patients. There were not very many of pure clofazimine alone. There were a number on prednisone.

Here are the new lesions, no data; no new

lesions; prednisone on, prednisone off, prednisone daily dose; thalidomide on, thalidomide off, and the daily dose of thalidomide. Here is a good response to thalidomide, with prednisone and thalidomide together. However, you can see that the thalidomide was gradually tapered over a year period, and was stopped at this point here.

The thalidomide, however, was carried on for another probably close to a year, 40-some weeks, and was stopped at this point. And, again, he recrudesced, had a lot of lesions when the thalidomide had been off. And then thalidomide was started again and his lesions returned to no new lesions.

Also, however, the thalidomide was continued here, once it had been restarted, and then it was dropped to 50 milligrams, and then to nothing. But with the second episode, there was no prednisone given. So, there were two pieces of evidence here that it was steroid sparing.

Then, for one last look, a little more complicated patient. This was a patient who had new lesions but was treated only with thalidomide for the first episode. Thalidomide was stopped. He was off thalidomide and off prednisone for the second episode. And then had what we can only infer was a pretty serious episode of new lesions. He was begun on prednisone, begun on thalidomide at a high dose of 200 milligrams a day, and the

prednisone was tapered. The thalidomide was continued for almost a year, and then the thalidomide was gradually tapered, till it was finished.

Although we do not have any data here -- all these points indicate no data -- our evidence is thalidomide was continued, as I say, for approximately another year, and steroid sparing was seen, because the steroids were stopped at this level and then carried, and the thalidomide wasn't stopped till 190 weeks.

So, that shows you the kinds of data that we got from the L.A. study.

If we looked only at the skin manifestations, not the systemic manifestations, I think we can say some things about the skim manifestations.

We can also learn a little bit about the dose. It appears that 100 milligrams is a good starting dose, as was mentioned by the company, but we really did not have much information on that. Probably 100 milligrams for 2 weeks, and if no response is achieved, raise the dose to 200 milligrams or to 150 milligrams, and then higher if necessary.

These data were derived from case report forms that were analyzed at the FDA by some people in this room, and we are very grateful for their work, because they did a very good job.

Now, we can't get much safety data out of this area. And you say, well, how can you say 52 percent, whereas this morning we heard 90-some percent?

Well, let me tell you, that is what I tried to stress this morning. People of good faith can look at the same dots on the same graphs and either see a response or non-response, and, more importantly, I think that what we see here is pretty good evidence of efficacy of the medication, that there were responses to the medication. 52 percent may not be great. It's a lot better than other things that we had -- at least in the thalidomide-alone group.

Some people might say, well, if you looked at these, and you might find that the data will change. If you look very closely at these, you find that they were on perhaps ibuprofen or aspirin or something else. They may have been on ibuprofen or aspirin, and that is why we stuck, again, to the skin lesions of ENL.

I think I'll stop at this point and see if there are any questions, Dr. McGuire. And I remember that this is your laser pointer.

DR. McGUIRE: That was important.

My preference would be to go ahead through the rest of the FDA presentations.

DR. WEINTRAUB: Good.

DR. McGUIRE: And to get my laser back.

(Laughter.)

DR. McGUIRE: I'm sorry, I didn't introduce the next speaker. He is Dr. Murray Lumpkin, and he will talk about the various distribution options.

DR. LUMPKIN: Good afternoon, ladies and gentlemen. I appreciate the opportunity also of being here with you this afternoon.

I do not want you to think, by our putting a point here of talking about different distribution options, that this in any way signifies a predetermined outcome, in the sense that we are talking about post-approval distribution here.

But as you heard this morning, one of the real issues surrounding the whole risk/benefit analysis for this particular product deals with one of the issues about how does one try to manage risk in the 1990s.

There have been a lot of parallels drawn today between life as it was in the 1960s when this product first came around and life as it exists now. Now, for many of you in this room, who are as old as I am, you remember the 1960s as the time that you went to grade school. But what I understand from the scientific approaches and the regulatory approaches that existed back in the 1960s, the big challenges that those individuals faced was, how do we

establish efficacy? How do we determine risk?

And these were challenges just simply trying to identify whether products really worked and what the risks were and how to identify those risks. And you see what happens when you don't have good, clean data to try to establish efficacy, and we've seen what happened with this product when you do not have good ways of trying to identify risk.

Now, that was a challenge that the people back in the 1960s were faced with. And I think when we look at the sophistication in drug development programs that have occurred in the last 35 to 40 years, we have become much better in learning how to identify risk.

But what our challenge is now is how do you communicate that risk and how do you manage that risk because it is not only an issue of identifying it and putting it into the equation because you know it happens, it is now an issue of saying, before you determine that equation of benefit and risk, if we know there are risks, are there ways that we can manage it so that the benefit is even perhaps better than what we thought it was, or at least in that equation.

So, hat brings us to the role, then, of restricted distribution and monitoring systems. This is something that is really very hard for us in this country

to deal with. It is kind of one of these quintessential American dilemmas of societal goals versus individual rights, and how do you balance those in a free society.

All of us are fairly familiar with how drugs generally get distributed in this country, and it is a distribution system that has served us well. If you think that once a drug is approved in the United States, very quickly thereafter you as a patient, your health care practitioner and your local pharmacist, no matter whether you are in Maine, Hawaii, above the Arctic Circle in Alaska, or Key West, throughout this entire continental span of land mass, that product is generally there and generally available without a lot of hassle for the patient, for the prescriber, and for the local pharmacist. And that is the way our system has served us well over the last century that we have basically had it.

So, now when we start talking about restriction distribution or modifying distribution to manage risk, it begins to raise a lot of whistles and bells and questions that people have to deal with.

As you've heard already today, this is something that, although it is not something we have a great deal of experience with in this country, it's something that we do have some experience with. And there are things that I think we have learned from the

experiences that we have had to date.

I am not going to talk a great deal about Accutane. You have heard about Accutane a great deal already today. This committee is very familiar with this particular program of trying to manage risk by a very large, heavy educationally oriented type of program. But it's a program that did have loopholes. And it's a program that is essentially around 10 years old now, and it's a program that I think we, as a community, have learned a great deal from.

As you heard this morning from the people from Celgene, I think they have tried very hard to look at this program and say, what were the good parts of this program, what can we learn from this program, and where were the loopholes, where did it tend to not accomplish its goal, and how can we try to make sure that does not happen if we do get an approval and go to a restricted distribution system in this country?

You've also heard about Clozaril and the program that that particular product had to try to manage the known risk of agranulocytosis with this particular product. I think one of the very important lessons that we learned from this particular program is that if you make it too tight up front, you might have great, 100 percent compliance, but you do get to the point where those

individuals who actually have to implement the program -- the physicians, the other health care prescribers, the patients -- they say no, it's too burdensome; it's not what we can stand on a day-to-day basis.

So, with Clozaril I think one of the things we learned, from the original program in 1990 to the program that we now have that came into being in 1992, is that you need to have a program that meets the needs of this very large country that we've talked about, that allows local areas to implement a quality assurance program to assure that the kinds of distribution controls that you have implemented indeed can be implemented by the pharmacists, by the health care practitioners, and by the patients who, in the end, are the ones whom we are all trying to serve.

Now, there is one other example that we have had that has not been mentioned. And it is a little bit different of a product, and that is the product called fentanyl Oralet. For those of you that know something about this particular product, fentanyl is a pain medication, a very potent pain medication, that has been available in this country for a great period of time.

There were problems with a patch version of this particular product, where the patch was being used in ways that put people at risk. And we did have some very bad outcomes because of particular off-label and

inappropriate use of the fentanyl patch. So, when it came time to look at a different formulation, which basically, for lack of a better word, was more of a Popsicle kind of presentation of this particular product for children, it was a tremendous advance in trying to come up with a formulation that allowed children to benefit from the benefits of this particular drug product, but it also made it, as a presentation to children that was obviously a presentation of a very, very potent, potentially dangerous drug product.

It was a product that primarily approved for use in hospitals as a preoperative product for use in very, very painful procedures and these kinds of things.

There was a program that was put into effect that basically limited its distribution to hospitals and institutions who had gone through a fairly rigorous educational program and who indeed showed that they had the resuscitative equipment available, that they had the staff available, and that, indeed, they could use this particular product in children in a way that they would manage the risk and perhaps very, very muchly decrease the potential risk of this particular product when it's used in children.

One of the points, though, I do want to make is that all of these three were basically done as a voluntary, cooperative kind of endeavor by the pharmaceutical

manufacturers who sponsor these particular products, very similarly to what you heard this morning. These were very responsible companies who have tried to look at this and say, what can we do, what can we realistically do to assure as much access to this product as possible for those who need, but, on the other side, to try to manage the risk in the best way possible in the 1990s?

Well, as we've looked at this, I do want to tell people that we do have a provision, and it's a provision in our regulations that we have not used yet. It is a fairly new provision. It came in as part of what are called the subpart H regulations. These are the regulations that deal, in one part of them, primarily with the accelerated approval of drugs under the surrogate endpoint provisions that we have used on several drugs thus far.

As you know, this particular group of regulations refer to drugs that treat serious diseases or that treat life-threatening illnesses, and they refer to drugs that provide meaningful therapeutic benefit to patients over existing treatments. Once you look at this group of drugs, then this particular series of regulations have two different components. One I have mentioned, the idea of saying that we are allowed to approve drugs that meet these definitions on a surrogate endpoint under the

accelerated approval.

Then the second part, not dealing with surrogate endpoints at all, basically says that if the agency concludes that a drug product is shown to be effective, but could only be safely used if distribution or use were restricted, FDA will require such post-marketing restrictions as are needed to assure the safe use of the drug product.

And then the regulations go forward and give just a couple of examples. It does not limit it to these kinds of restrictions, but it gives these as examples. And they are very similar to the kind that had been worked out previously with the products that I talked about, or the kind that one sees that the company this morning talked about in their proposed distribution plan.

For example, restricting distribution to certain facilities or to certain physicians or other practitioners who have special training or experience, or distributing the product on the condition that there be performance of specified medical procedures.

So, this idea of having a restricted distribution system, although one we have not used frequently in this country, it is one that is in our regulations, it is one that we can use. I think it is one that, when we have not used it in a mandatory sense, but

when we have used it in a cooperative sense, in a voluntary sense with the sponsors, we have had a period of learning over the decade of the 1990s.

What you saw today, I think, is the beginning of the discussion of taking the bits and pieces that we have learned from Accutane, that we have learned from Clozaril, that we have learned fentanyl Oralet, and said, now that we look at this product, how can we manage, how can we communicate the risks that we know about thalidomide to the patients, to the practitioners, to really try to manage this risk such that the benefit will be available to those who need it?

That's our spiel on the ways that we can look at restricted distribution at this point in time. I give it you in the audience, I give it to you on the committee, as just a foundation to begin the discussion of the proposal that was put on the table this morning by Celgene as we get to the questions tomorrow. And if we get past the basic efficacy and safety and the recommendation is that people feel that the benefits outweigh the risks, then we can further get into a discussion of how to manage those risks under these kinds of provisions.

I thank you for your attention, and now Lou Morris is going to talk to you a little bit about looking at the Celgene proposal -- just some other ideas that we

had had as we had begun to look at this, that might enhance their proposal a little bit further.

DR. McGUIRE: For those of you who do not know Dr. Morris, he is the supervisory psychologist in the Division of Drug Marketing, Advertising and Communications.

DR. MORRIS: Thank you. Good afternoon. It is a pleasure to be here.

We heard this morning from Mr. Williams about Celgene's STEPS program. It is a system for thalidomide education and prescribing safety. I think the fact that it's a system is very important. It shows that it is thoroughly thought through. There are three elements to it that I discern.

One is the communications elements. And that is composed of a series of brochures and a consent sheet that's very thorough. I think if one reads through these materials, one clearly gets the concept that this is a very thorough message. It's very consistent. It's very concrete. I think it clearly demonstrates that the message is there.

If one looks at the distributional elements of it, I think it's very innovative in that it uses not only pharmacies that agree to keep a system in place, but it actually uses a consent sheet and the pregnancy test as tickets that people need to get their medicine. It

certainly goes beyond existing programs.

A third part of the program that I think is very important is that it sets up at least the potential for a quality control check. I think the mandatory registry is very important in that regard. I think that we should be humble enough to realize that we cannot, up front, design a perfect system, and testing it and making sure it's right is something that is very important.

However, we've heard and we will continue to hear some concerns, and here are some that we have discerned.

The first thing is consumer understanding. These are some very, very difficult concepts for people. And we do know that the literacy of the population is something that suggests that at least 20 percent of the population have an awful lot of difficulty reading anything, and another 20 percent are sometimes considered functionally illiterate, because, even if they do read, they have difficulty with complex concepts.

The solution is not making something at a third-grade level. It is explaining it well enough so that people have a true understanding of the information.

A second concern is that the people who will be obtaining thalidomide -- it is a whole new world out there. When I say the word "thalidomide," I think people in the

audience here conjure up very vivid memories, as Mary Pendergast mentioned. The median age in the U.S. population is 35. Most people weren't born when the thalidomide tragedy occurred. I have a little bit of data I will be sharing with you in just a second on that.

The third concern is, although the system is thought through and is well designed, real questions on how health professionals will follow through with this, it is just unclear. I think we are asking an awful lot of health professionals.

How will the system actually operate? I think we have to pay attention to that.

Here is some data. We have started a study on over-the-counter drug labels. The study is being conducted in eight shopping malls around the country. And as of 5 o'clock last night, we have been -- this is literally hot data. We asked a very simple question in that survey, and that was, we asked people, could you define what the word "thalidomide" was as if you had seen it in a dictionary? And what percent would even venture a guess?

Overall, about half the people said they don't know. This is just the females. We wanted to see if there was a gender difference. There were 77 females. Just as you would expect, age breakdowns. The people who were in the younger age groups didn't know or were wrong. People

who were over 40 were more likely to get it correct or partially correct. So, half the people do not know what thalidomide is. It's just what you would expect.

The next one for males is a very similar set of data. We didn't see any obvious visual differences in looking at the data. But, again, young males don't know. Older ones are more likely to get it right.

These data are highly preliminary. We will be continuing to collect it. It is only 130 subjects, so it is not conclusory. But I think it does suggest what we expect, which is that there is clearly the age difference. And you just cannot assume that when you say the word "thalidomide," there is a vivid memory, and I think a vivid memory is very important in terms of how people are going to use this product.

Yes?

DR. DUVIC: That is really interesting data. And given that data, shouldn't we just have the word "thalidomide," and not have two different names for this drug? Because Synovir sounds like an antiviral for herpes or something. For the purpose of educating the public, which is going to need to be done for this, shouldn't it just have one name, and that name be thalidomide, for historical reasons?

DR. MORRIS: But half the people do not know

what thalidomide is.

DR. DUVIC: I understand that. And so even less are going to know Synovir, once you start having a new name for it.

DR. MORRIS: Well, I think it is important to have a clear communication objective. How we do that is something I think we can -- you know, we are willing to listen to those suggestions at this point. But I do not know. You mean not have a trade name on it? Is that what you are suggesting?

DR. DUVIC: That's right.

DR. MORRIS: Well, I think that's something the committee should certainly debate.

DR. McGUIRE: That's something that was discussed at the November meeting.

DR. MORRIS: Okay. Well, let me just raise some ideas and some suggestions.

In terms of how people use this product, one of the things that I am concerned about in terms of what Celgene is suggesting is that they are suggesting two means of education. One is health professional counseling and the other is a series of written information. I think that having something in between -- audiovisuals, a tape or something like that -- I think could be a tremendous improvement here for a couple of reasons.

One is I think it is just very important to have a very vivid message. I do not know if written communication does that. Having and audiotape that people can think about and envision and explain things, I think can be very important. I think it could be integrated to the informed consent process, and I think it is something that we should think about.

The next suggestion, and I think it is something that we have heard this morning, is that health professional incentives and training is very important. One of the things I liked about Celgene's proposal is that they use the word "system." And I think if we think of this as an error prevention analysis system that we do in medication errors -- a way of not thinking about individuals, but thinking about a systems approach to prevent errors -- is a nice way to think about it. And I think that having health professionals integrated into a system would be a way to decrease the likelihood of some error occurring.

The third concern, and I guess a suggestion for some vigilance, is simply to think about quality control not only in terms of the initial system, but what is going to happen over the long term. One of the things we know about behavioral compliance is that written information can improve short-term compliance, but long-term compliance is

very hard.

So, I think, as part of the quality control, to worry not only about the people who initially get it and what they understand but, over the long term, what do they actually do.

Those are some of the things I would like to suggest.

I thank you, and I would be happy to answer questions.

DR. McGUIRE: I know there are many questions from the committee. I would like to have a micro-break and reconvene at 3:30. Please have the presenters from the FDA back at 3:30, and we will have the committee, so we can get directly into the questions. There are lots of things to be answered.

(Recess.)

DR. McGUIRE: Ladies and gentlemen, I would like to reconvene the afternoon meeting. Please, can the committee be seated and the representatives of the agency.

First, I would invite questions from the advisory committee to the representatives of the agency: Drs. Wilkin, Hill, Bashaw, Weintraub, Lumpkin, and Morris.

Dr. Bergfeld.

DR. BERGFELD: Yes, I have a question of Dr. Dennis Bashaw, and that has to do with the metabolites.

I understand from all the presentations this afternoon and even this morning that the metabolites of thalidomide are not totally known, nor is the mechanism of metabolism or excretion totally understood. And I wanted to know what would be recommended to understanding this better.

DR. BASHAW: The way it is normally done, and the way it has been done in the past in this area, we try to use in vitro data and in vivo data to come up with different approaches. And we thought that the study we had in the Hansen's patients, looking at the parent and the three, what we considered, most likely metabolites -- and this was done in consultation with the sponsor and their consultants -- would be an appropriate way. However, as you know, it didn't work out.

The next step to go to, or one to consider, would be, of course, to use a radio-labeled trial, most likely with a carbon-14 label, because if it does undergo hydrolysis, putting a tritium label on there would be the last thing you would want to do, because it would just go everywhere as part of the hydrolysis process. But that would probably be the next step if the committee felt that we should pursue it further -- would be a carbon-14 study.

DR. BERGFELD: Well, I need to ask a follow-up question. I don't understand that we would consider a drug that we did not understand its metabolism in some way, when

it has such a terrible outcome if given to specific women.

DR. BASHAW: Well, I think we do know some about the metabolism. I don't think it is totally a black box, although one can quibble about some of the P450 information, but those in vitro studies clearly indicate that the major routes of drug metabolism, it does not participate in, and that the product should be ones of hydrolysis.

As I mentioned in my presentation, in my review, there is an article I extracted. I think it proposes something on the order of 18 potential hydrolysis metabolites. And that certainly multiplies the difficulty. You get small amounts, a few percent here, a few percent there.

Normally, yes, we certainly do know more about metabolites. But, oftentimes, when we do approve drugs, we have just general ideas about metabolism -- maybe 30 or 40 percent identified, not 100 percent identification of metabolites. That is really very rarely accomplished that we know exactly what it's always broken down to.

I think that where hydrolysis is a major mechanism, and again, if you look at the structure of thalidomide, it has got all those carbonyls hanging off of it, that it has got so many places for hydrolysis to grab onto, it just really complicates the matter. And that is

what defeated our earlier efforts. We made an attempt, but it just didn't work.

DR. BERGFELD: Well, can I ask you another question?

Would that same be the answer for not knowing enough about how it is eliminated?

DR. MORRIS: I'm sorry? Could you repeat that, please?

DR. BERGFELD: Your description of why the complication of understanding its metabolism and the need for another study or studies to understand that, is that the same answer that would be given for understanding the elimination?

DR. BASHAW: Yes, ma'am.

DR. McGUIRE: Dr. Orkin?

DR. ORKIN: I would like to ask a question of Louis Morris. I asked him this just a moment ago, but I thought I'd put him on the carpet. And that is, is it possible to design a very simple exam that a person would have to fill out before they get the prescription? And maybe that should have done with Accutane.

DR. MORRIS: Yes, sure, anything is possible. In fact, I would suggest, if you look at the informed consent sheet, one of the items says, I understand the material. And how do people know that, if they understand

it or not?

I think building that into the health professional counseling would be a good way of doing, so a health professional can assess the extent to which people do know about the product and understand its risks and ask question in an open-ended way, to check people's understanding. I think that is something that could be designed into the program.

DR. ORKIN: And maybe that could be a follow-up to your suggestion about the audiovisuals, to see that they do comprehend this.

DR. MORRIS: Yes, I think if it is done in a way that involves the patient, the more the better.

DR. McGUIRE: Dr. Shannon?

DR. SHANNON: Yes, I would like to make a comment.

There is a heck of a lot known about the metabolism of this drug, quite frankly. This has been presented. And it is very labile at the amide binds, and we know right where it hydrolyzes first and what are the products. So, in the literature, in the early heydays of thalidomide, it was looked at thoroughly, so there's a lot known.

What I would like to share -- and it was very nice to see these elegant slides, with all the

pharmacokinetics and so forth and doses, and it was also good to see this confirm what we know previously, and that is that you achieve about a maximum blood level of about 1 to 2 micrograms, despite the regimens that you take.

The other thing is that Dr. Kilpatrick had mentioned about a low zone tolerance, as far as -- and I am maybe reading too much into his question -- but it has been known that ingestion of one 100-milligram tablet of thalidomide during the first trimester of pregnancy caused a fetal malformation.

The other thing that is the other good side of thalidomide that Dr. Hill had alluded to was possibly aspects of poor solubility with the aspect of 60 micrograms being the maximum solubility constant of thalidomide in water. What I would like to also suggest is one of the reasons you cannot, presumably -- and I do not know this factually -- but one of the speculations is the reason you cannot overdose with thalidomide is very simply that it forms diamers. It forms diamers in the gut, and these are most likely eliminated quickly. And if it is absorbed in the GI tract, those are probably eliminated more quickly. There have been cases where people have tried to take grams to overdose with thalidomide and have not had any problems.

The point also that has made a lot, again, with doses. It looks like the maximum blood level achieved,

despite the regimen, is 2 to 3 micrograms per ml, where maybe in GBH reaction, where they have got some problems with gut motility, you might achieve 20 to 25 micrograms maximum. Whether or not that's relevant for clinical efficacy and so forth, but that is generally considered to be the plasma hydrolysis concentrations of thalidomide.

But, again, in point of fact, there's an awful lot that is known about the metabolism and so forth and the breakdown.

DR. McGUIRE: Mr. Warren?

MR. WARREN: I guess I would like to address my comments to Mr. Morris and that is regarding the education plan and everything that I had seen about the lack of education on behalf of American women. From a preliminary point of view, 48 percent of them didn't know what thalidomide was. That frightens us, obviously, from the Thalidomide Victims Association of Canada.

So, should this ever be licensed, I would just suggest -- I liked what I saw about audiovisual communication and that kind of thing -- and I would suggest that that maybe is a role, where the victims of thalidomide should certainly make the impact statements that would be useful.

My question comes down to the various distribution options and how that is actually implemented.

I liked better what I saw under mandatory regulations. I think it would have more teeth. So, my question comes down to, is it really a difficult thing to go towards a mandatory distribution process over a voluntary distribution process?

DR. McGUIRE: You are looking at me, but you're talking to Dr. Lumpkin I think.

MR. WARREN: Yes; I'm sorry. I am looking at you because that is who I was addressing.

DR. WOODCOCK: I'm Janet Woodcock.

The need to impose a mandatory restriction, under regulation, depends on our judgment of whether that is necessary to ensure the safety of the product. So, it really depends on how safe we feel the safety would be under a voluntary system or whatever safety is available compared to the need for additional safety that would merit, that would require for approval a restricted distribution.

DR. BERGFELD: Could I ask what drugs are under the mandatory distribution?

DR. WOODCOCK: There has not been any, as Dr. Lumpkin said. There have been no drugs approved with that part of those regulations to date.

DR. McGUIRE: Dr. Kilpatrick, you have been very patient.

DR. KILPATRICK: Thank you, sir.

I'd like to ask two questions, following up on both the remarks that have been made recently. One, again, to Dr. Lumpkin, about restricted distribution. Does the agency have the authority to withdraw approval if restricted distribution is not working?

DR. WOODCOCK: Under the accelerated approval regulations, there are provisions for more rapid withdrawal of approval. Under our ordinary regulations, under ordinary approvals, it is somewhat difficult for FDA to rapidly withdraw a drug from the market. It is usually voluntary by the manufacturers. But we can do it.

DR. KILPATRICK: But we are talking over a long period about a system which may degrade or deteriorate over time, and we're talking about a monitoring system which may be very effective initially. But my concern is that, if we go this direction, the agency may in fact be in the job of monitoring a monitoring system, which is getting rather laborious.

Coming back to the other question about dosing, do I take it, sir, that there is no such thing as an optimal regimen for the treatment of ENL with thalidomide, from what you were saying?

DR. SHANNON: I am not in clinical medicine, and I wouldn't speculate on that. I just know that for

severe ENL, generally 100 milligrams, four times daily, is what's started off. And I would have to refer that to Dr. Rea and Dr. Yoder. But each physician has his own particular regimen. But that is probably the highest dose.

The problem is you are hearing thalidomide being recommended be used at gram quantities in one ingestion time. My thoughts on that would be it is probably a waste of the drug, in the sense that it is going to just be excreted or through the gut, and so forth.

DR. KILPATRICK: Dr. McGuire, is this something that the sponsor will be undertaking? I know it may not be required by FDA, but have they plans to go forward beyond the current Philippines study of 100 versus 300 milligrams into what might be a more effective dose regimen?

DR. McGUIRE: Of course, I do not know the answer to that. The Philippines is in process. It is not complete by any means.

DR. KILPATRICK: I am asking actually do their plans go beyond that? That will certainly not answer all of the questions that it might raise.

DR. McGUIRE: I think if the agency asked them to go beyond that, they will.

DR. KILPATRICK: Thanks.

DR. McGUIRE: Dr. Woodcock.

DR. WOODCOCK: Thank you.

I just wanted to clarify something you were discussing about ongoing safety and monitoring a monitoring program. Just as we have with many other drugs, the experience in the marketplace may reveal that the safety of the product that was believed to be present in the pre-approval evaluation, the product is less safe when it gets on the market, there are unexpected adverse reactions, or sometimes there are other kind of problems, such as failure of the safeguards that were put into place.

So, this is not an unusual or unexpected situation if it were to occur, and we have to take measures. I believe some products have been brought back to this advisory committee sometimes because of safety problems that have occurred post-marketing. So, that would be something that we would expect to happen.

DR. KILPATRICK: Thank you.

DR. McGUIRE: Mrs. Cohen.

MS. COHEN: Dr. Lumpkin said he went to grade school in the 1960s. I would hate to tell you when I went to grade school.

(Laughter.)

MS. COHEN: But I have some historical memory of DES and Norlutin and the problems that it caused.

I also, in another life, which I do not even think the members know, was a licensing coordinator and

program certifier for group homes for the developmentally disabled and the mentally disabled. And I can tell you, I've seen the traumas that it causes in families and the disruption and the divorce and everything else that goes with it. So, I have this in my mind, and I would like to have it dispelled. And I hope we will be able to do it.

I have a couple of questions. One, I am going to put my foot in my mouth, but the other one I did already.

DR. KILPATRICK: The other foot?

MS. COHEN: The other foot.

(Laughter.)

MS. COHEN: It was bungy jumping, believe me.

(Laughter.)

MS. COHEN: There are people who do not believe in abortion, and they have a right not to believe in abortion. When you question people or have these lists of things, is that going to in any way affect how you feel about allowing them to use thalidomide? And what if someone does need an abortion, how is that going to be dealt with?

And I will ask the other question, because it has been in my mind -- two more questions actually. Thalidomide did come into this country through buying clubs. Is there any information available on what happened

to that use of thalidomide, in terms of teratogenicity and neurotoxicity? I would like to know that.

And, finally, with due respect, I am sitting here and I am thinking in my mind that you are going to a great deal of effort. And I understand we only have approximately 200 cases of leprosy a year, and that is 200 too many. Are you anticipating using another use of your drug, and should you share it with us now so that we can understand and you won't have to come back and come back and come back again and maybe can encompass it all the way?

DR. McGUIRE: To whom was that directed? Were you directing that to one of the sponsors?

MS. COHEN: Yes, absolutely.

DR. McGUIRE: Would anyone from Celgene like to respond to that? Jerry?

DR. THOMAS: Hi, Steve Thomas again.

I'll take a first approach actually at answering a very important question, Mrs. Cohen.

As I think we tried, or I tried, specifically to point out, our company is actively, extensively evaluating the use of this agent in a number of other life-threatening indications. AIDS wasting is mentioned, aphthous ulceration in HIV positive individuals, and graft versus host disease.

If the efficacy and the safety of the drug in

these indications is clearly established, we would intend to provide information in a range of NDA submissions, which, again, would fall to FDA and other committees actually to evaluate.

How the drug is used is handled through, initially, the labeling of the compound and is quite clearly legislated for and directed under the regulations and the FDA. Our company is only able to make our compound available under the directions that we receive actually from FDA.

We are in a position whereby we think this compound may have a variety of uses in a range of indications. Each of the risk-versus-benefit equations has to be established independently in each of those indications.

I wonder if actually Bruce Williams would like to add anything?

MR. WILLIAMS: No, except that, again, the proposal that we have made for the distribution system, in fact, was carefully considered because of the knowledge that usage might occur in other areas while these other indications are being developed, and that if that usage were to occur, it had to be captured by the system and could not be allowed to be occurring outside of the system without monitoring and follow-up.

DR. McGUIRE: The other piece of Mrs. Cohen's question was, have there been any birth defects in the orphan use applications or in the buyers' club usage? And the sponsor may or may not know that, and perhaps the agency knows that.

DR. THOMAS: Well, all that, obviously, our company is able to work with is the information on the exposure of our compound. It is clear from the information that we have that that has not occurred. I don't know if we have any more information from buyers' clubs at this meeting.

MS. COHEN: Have you sought the information?

DR. THOMAS: Yes we have, indeed. However, I would feel uncomfortable answering a question on behalf of a range of agencies that I haven't had an opportunity of addressing.

MS. COHEN: And I would be uncomfortable not to know.

DR. THOMAS: I think that you have a perfect right, actually, to ask that question. I'm not sure that we can address that question right now. However, it is totally possible that, over the course of the next few days, we can do that.

DR. McGUIRE: Let's give Dr. Woodcock a chance the buyers' club question. Do you have any information on

that?

DR. WOODCOCK: We do not know of adverse pregnancy outcomes that have occurred as a result of the illegal distribution of thalidomide. Obviously, the reporting of even adverse events of approved drugs we know is under-reported, and it is very likely that drugs that are not being distributed in legal channels, that it would be more likely to be even more under-reported. Nevertheless, we have received no reports.

DR. McGUIRE: Dr. Mindel, do you have a question?

DR. MINDEL: Yes.

With drugs that aren't orphan drugs, in evaluating the data that is presented, there's a basis of what the FDA requires that is sort of in the back of my mind. I think of these two good controlled studies or is this a good multi-center study, and things like that. But this is an orphan drug, and your reviewers have said that it doesn't meet the criteria for approval. And I assume that the reason we are discussing this is because it's not expected that an orphan drug meet the criteria of a drug that isn't an orphan drug.

I'd like to know, though, what are the criteria. Are there any internal criteria -- I am not aware of what they are -- by which an orphan drug is

approved? And could you tell us how this data compares with, say, the last one or two orphan drugs that were approved? Were they controlled studies? Were they required?

DR. WOODCOCK: Yes, the requirement in our law, in our statute, is for substantial evidence from controlled trials. In many cases, however, in diseases of very low prevalence or in other circumstances, where randomized controls are not possible or haven't been performed, we look at historically controlled data.

In the literature submission, there are several control trials that are submitted that we have not had full access to the primary data, or when we went back to the primary patient records, the data were very confusing. So, those trials aren't, in themselves, totally adequate, as was revealed by the reviewers' comments.

However, we have additional historically controlled data in this case. The issue always with historically controlled data is whether or not you have enough confidence in your understanding of the natural history of the disease and the response that you see in response to treatment that you can make a reliable inference that the drug is effective.

So, we have approved quite a number of drugs on the basis of very small data sets, sometimes with surrogate

endpoints, often with historically controlled data for rare diseases. That's correct.

DR. MINDEL: So that you would say that the data is compatible with other approved orphan drugs in the past -- the quality and the caliber and the quantity of the data?

DR. WOODCOCK: Certainly. But what we are asking you is are the inferences -- are you going to advise us about the reliable inference that you can make from that about a treatment effect, the presence of a treatment effect from those data? The fact that they are historically controlled or the fact that we do not have access to the primary data sets are issues that we have dealt with in the past, yes. They have to be taken into account. They decrease the reliability of your inference.

And up against that might be the fact that there have been multiple observations in numerous hands of this treatment effect and other things that we want you to take into account when you advise us.

DR. McGUIRE: Thanks very much.

We have some other important presentations that I don't want to compromise because of time. Mr. Warren, if you wanted to make one last comment, then we will go to the next presentation.

MR. WARREN: Yes, I did. And now that I have

heard many presentations today, I will be making a lot more comments.

My question follows up on my previous question, because I wanted that information. Can you license a drug in this country -- and, as I understand, the answer is going to be yes. Can you license a drug in this country on a condition basis, so you are licensing for leprosy? And can a mandatory restriction be put on that so it's only used for that condition? And then, should you receive the efficacy or all of the data regarding the next use, then you would license it strictly for the next use?

Because we have strong concerns -- and Mrs. Cohen is the first person that has expressed it in a way that I could digest and really get into -- and that is regarding off-label. That certainly is my belief firmly. And I may be inappropriate in stating it, but, really, I think we should be dealing with the off-label issues. I really do. I think we are going a long way around.

The second part is -- and I know the answer to this as well -- there have been no long-term studies conducted on our mothers, who took this drug 40 years ago, and nobody has chosen to study the long-term effects on them. Wouldn't that be useful data? Because those persons who may take it today may survive whatever illness or may live long term and never have to take thalidomide again,

and wouldn't we like to know what the long-term effects would be on those populations?

And my last point, because I thought it was also very important, is we have always advocated, regarding abortion, is that it should be a person's choice regarding that regard. But our concern comes from a different point. And that is that people should not be forced to sign anything that would force them to have an abortion should a thalidomider be born, and that is what we call ourselves, because we have some quality of life and some right to be here.

Thank you.

DR. McGUIRE: Dr. Bashaw, you had a comment?

DR. BASHAW: Yes. I would like to make a clarification, if the committee would indulge me, about a comment I brought up during my presentation with regards to the drug interaction study with oral contraceptives. I alluded to the fact that there are some changes going on in that area and I have been asked to clarify that.

When the protocol that was done for thalidomide was developed, it was approximately a year and a half, almost two years ago. And it basically involved looking at the pharmacokinetics of the various combinations -- ethinyl estradiol and norethindrone and also thalidomide, and looking for kinetic interactions. Obviously, there is also

pharmacodynamic measures which can also be taken -- FSH, LH, and other tests which can be done.

Since this protocol was initiated, there have been discussions between the Dermatology Division, with the reproductive side of the FDA, and also the Division of Biopharmaceutics, Clinical Pharmacology, looking at ways of improving the study design and making a better protocol.

And that is what I was alluding to in my presentation, that, in the future, we will be coming to this committee with a different protocol for your consideration, since this committee does have a lot of experience and a lot of concern in this area, trying to look at a study design which incorporates both pharmacokinetic and pharmacodynamic measures. Because there could potentially be the possibility -- not necessarily with this drug, but there is always the possibility that while there was not a kinetic interaction, there could be dynamic interaction. And that is what we'd be most concerned about.

So, that's the clarification I just wanted to offer. The study itself that was done with this NDA is acceptable, but we do have new thoughts that have come up since the study was initiated, and we are moving forward with new protocols, with others sponsors right now.

DR. McGUIRE: Dennis, thanks very much.

Let's go to the next presentation, by Dr. Cynthia Moore, on birth defects due to thalidomide exposure, CDC considerations.

DR. MOORE: Before I begin, I would like to mention that actually the most important word in the title of my presentation was omitted. And that word is "preventing." It goes at the beginning of the title.

I do want to thank you for the opportunity to attend and to participate in this important meeting. The Centers for Disease Control and Prevention entered this arena because a major part of the Division of Birth Defects and Developmental Disabilities' mission is to improve the health of American children by preventing birth defects.

To a great extent, our division owes its existence to the tragedy that was the first thalidomide epidemic and we, as well as others, do not wish to see it occur again.

In March of this year, CDC sponsored a workshop in Atlanta entitled "Preventing Birth Defects Due to Thalidomide Exposure." We were fortunate to have participation by individuals from many different areas of expertise, including our federal colleagues from the FDA and NIH, many pharmaceutical companies, professional practice representatives, academicians, and others.

The purpose of this meeting was to provide a

forum devoted to the discussion of the teratogenic effects of thalidomide and methods to limit fetal exposure to this drug should it be approved for use. This meeting was not designed to develop a consensus on this issue, and no attempt was made to reach one, but merely to gather individual suggestions by the meeting participants.

Although other adverse effects of this drug are known or suspected, the CDC meeting addressed only the teratogenic effects. I believe we all are well aware of these birth defects. We know that when this drug is used by women of childbearing potential, the risk for causing serious birth defects can never be lowered to zero. In situations where there is indiscriminate use of the drug or poor control surrounding its use, as in Brazil, infants with thalidomide embryopathy are being born.

May I have the first slide, please?

This infant was born approximately two years ago to a Brazilian mother who received thalidomide for leprosy. He has the typical limb malformations that we see associated with thalidomide exposure.

For the 5 patients at the Hansen's Disease Center in Carville, Louisiana, who are currently receiving thalidomide for treatment of ENL, the teratogenic risk is small, especially since 4 are males. The risk may also be lower for individuals who are buying thalidomide through

buyer networks, since I understand that members of these clubs are also primarily male.

Incidentally, as of yesterday, the buyers' club group in Atlanta was very active and willing to sell thalidomide.

The CDC meeting considered not only the teratogenic risk for individuals with ENL, but also the risks that this approval could bring to a population of patients with other disorders for which treatment with thalidomide has given beneficial results. There isn't time to present everyone of the dozens of suggestions we heard at that March meeting. Our staff considered all of them, and extracted those which we thought would be most effective and practical in preventing fetal exposure.

In the form of draft recommendations, these suggestions have gone out for comment to the meeting participants and are now under revision. I'd like to highlight some of those suggestions for you this afternoon.

We noted that virtually all of the suggestions to prevent birth defects centered around the concepts of limiting the use of the drug, educating health care providers and patients about the use of the drug, and monitoring those who were using the drug. These concepts were summarized by CDC staff into these five proposed recommendations, focused mainly on women of childbearing

potential.

These are that patients should be suitable candidates for thalidomide. They should be educated and counseled about the teratogenicity and about contraception. The drug should be packaged and dispensed in a manner to minimize both inappropriate and inadvertent use. Prescribers and dispensers should be well-educated about thalidomide and its use. And patients should be monitored during use to reduce the risk for fetal exposure.

When considering if a woman of childbearing potential is a suitable candidate for thalidomide therapy, we thought these four points were very important. The most difficult issue has been the first point listed, for it seems that most would agree with the other points -- that a prospective patient should not be pregnant at the initiation of therapy, should have access to and be a capable and effective user of birth control, and should understand the risks associated with using this drug.

However, when to use the drug is the question. It was suggested at the meeting that the drug should have not only been proven to be effective for the condition, but because of the severe risk, other options -- hopefully, non-teratogenic -- should have been tried first, if available.

Since approval of a drug for a specific use

must be based in part on its effectiveness, it was also suggested by some meeting participants that the common practice of off-label use of drugs be prohibited for thalidomide. Again, this is controversial, but it would limit exposure at least until other indications are approved.

Patients should, of course, be counseled about the teratogenicity. In all patient education activities, the concepts of appropriate and pre-tested messages, with post-educational knowledge assessment, are included. Several meeting participants stressed the need for inclusion of photographs of affected infants. And we have heard that again today. The line drawing of an infant with Accutane embryopathy that is included in the Roche pregnancy prevention program was thought to be inadequate.

Also, avoiding possible fetal exposure caused by sharing pills or taking left-over pills necessitates counseling all patients about the teratogenicity and the importance of not keeping unused pills.

The choice of an effective contraceptive approach, particularly for individuals with a chronic illness, can be a challenging effort according to our OB/GYN colleagues. It was suggested that this practice be limited to those providers with expertise in this area. Although consistent and proper use of contraception is the

goal, unprotected intercourse could occur under a number of circumstances. This topic also elicited many comments from our meeting participants, since we proposed that emergency contraception be discussed and prescribed.

At the very least, as one of our participants suggested, female patients of childbearing potential who have unprotected sexual intercourse should stop taking thalidomide immediately and not resume until they have been evaluated and found not to be pregnant. This same suggestion would apply to women who are uncertain about the effectiveness of their contraception at any point in time.

I would like to acknowledge Sally Cooper, from PWA, who gave us this suggestion, since she so graciously earlier gave up her time.

Packaging suggestions included labels that state "causes severe birth defects" and the word "thalidomide." How recognizable the word "thalidomide" is to individuals in their 20s or 30s who may be patients or even health care providers was not known to us, I guess still is not known to us, but we have a little information on that given today.

Other ideas such as blister packs and use of a tested symbol to denote no use in pregnancy were also discussed during the meeting.

Although we've received both positive and

negative feedback about these suggestions on dispensing, the last two stimulate the most discussion, mainly pertaining to the idea that the pharmacist would also be a gatekeeper for thalidomide and in some ways serve as the ultimate control over who receives the drug. This is not an idea without precedent. For at least one drug, Clozaril, dispensing cannot be done unless the pharmacist is presented documentation of requisite laboratory results.

The most notable point under this heading is the suggested concept that prescribers and dispensers should do more than just register to obtain the privilege. Education and knowledge assessments should be connected to this privilege, a privilege which also could be revoked. The development of specific practice guidelines by professional groups was also suggested.

Monitoring suggestions pertain to follow-up of the female patient while on therapy by her health care provider and referral for specialized counseling in the event of an exposed pregnancy.

In addition, a more global monitoring of all women of childbearing potential through the establishment of a prospective registry was suggested. This registry would follow all women of childbearing potential on thalidomide for fetal exposure and outcome of the exposed pregnancies. The registry would provide information to

determine the magnitude and hopefully the source of prevention failures.

That is the last slide.

I've given a brief overview of the suggestions from the CDC meeting Preventing Birth Defects Due to Thalidomide Exposure. As an encompassing summary, we were told that the most rigorous pregnancy prevention program yet described, the Roche pregnancy prevention program for women on Accutane, was a good starting point but not rigorous enough for a teratogen as potent as thalidomide.

Evaluation of this program has shown that some women received Accutane without a pregnancy test, pregnancies did occur during therapy, and affected fetuses were aborted or went on to live birth. Unfortunately, even with a stronger program for thalidomide, some affected infants will also be born.

We would like to thank all the participants in our meeting. Several of them are here today. Our Birth Defects Group at CDC is eager to further explore suggestions from the meeting and work with all parties to develop a prevention program that hopefully will assist women who receive thalidomide, their partners, and their health care providers in preventing these serious but preventable birth defects.

Thank you.

DR. McGUIRE: Thank you, Dr. Moore.

We have time for a few questions. Dr. Duvic?

DR. DUVIC: Thank you very much for the presentation.

I share Dr. Bergfeld's concerns that we do not know yet about fat storage and lipid solubility of this drug. For etretinate, the drug can hang around in fat for as long as a year. If this is the case for something like thalidomide, then stopping the drug on day 1 of pregnancy would have no effect. So, before we could even consider using this drug in women of childbearing age, we would have to have that data. And I have heard no one answer that question today.

DR. MOORE: I agree with you. The preliminary data that we looked at, which was slim, suggested that it was rapidly removed from the body, but I do agree with you totally that you would need to know that information. Actually the drug that you mentioned may hang around for many years.

DR. MATHEWS: In follow-up to that same point, do you know if there's any epidemiologic evidence that could address that question from the initial epidemic? In other words, women who took the drug prior to pregnancy at varying intervals of time prior to becoming pregnant and whether there were any detectable cases attributable to

that type of exposure.

DR. MOORE: I don't know that for certain. I have not read any account of that in the considerable literature that there is, but a lot of it is -- how shall we say -- cases that were gone back and looked at much later, and whether or not there is ability to pull out individuals who may have been exposed in this manner, I don't know from those older papers. I don't know if there's anyone else here in the audience that could answer that question. I really can't.

DR. McGUIRE: I think we have seen data indicating that there is a particular period, after implantation, of peak sensitivity. Of course, my memory is not good enough to remember where I saw it or read it.

Does the sponsor know about that? Did I read it in the black book? Okay.

DR. MOORE: That is true, absolutely true, that there is a critical period. But I think what the questioner was talking about is women who stopped use prior to this critical period and would the drug hang around long enough in some body tissue to actually cause a problem.

DR. THOMAS: It's actually Steve Thomas again.

It is a valid question. The information that is highly consistent in the literature across humans and other species is that there is a narrow window which has

been described after implantation where the fetus is apparently highly susceptible to harm.

Yes, it is important to note that if there were a problem associated actually with the drug hanging around longer than would otherwise normally be expected from the data that we have actually presented and also from the extensive literature, we would not be able to make a comment on that window because that window would actually be highly susceptible to a variability of the drug leaching from fat stores, which we just have not seen.

It is a very valid question. There's nothing in the literature that we are aware of -- and we have looked at all of it -- that would indicate it is a problem. I think that's all I can say on that issue.

DR. McGUIRE: Dr. Kilpatrick had a question.

DR. KILPATRICK: Actually, sir, two questions of Dr. Moore.

A long time ago I was involved in a WHO international study of fetal abnormalities. I don't think this occurs, but there's no such thing as registration in the United States of fetal abnormalities, still births and live births? Can we come at it from another direction and come at cases and go back and look? But is there such a registration or any demographic requirement?

DR. MOORE: Well, there are multiple birth

defects surveillance systems that exist in the United States, and there is one in Atlanta that is run by CDC in the metropolitan area.

I think this would be a very difficult question to answer using that mechanism when you may be talking about a difference of a few days. The critical period that we're talking about is the period of organogenesis, and it's a critical period for exposure to any teratogen.

I would like to add that we really don't, I think, have the answer to whether there are problems with later exposure after the organs have formed, but the central nervous system is still developing in a fetus up to term. There have been some reports of children with functional problems such as mental retardation. At present those babies I believe have had other birth defects that were fairly typical of thalidomide embryopathy. In babies who had just these functional problems alone, it was questioned whether or not it was due to thalidomide.

But I'm not totally comfortable saying that just using thalidomide in that early period of organogenesis is the only time that you could do harm to a developing fetus.

DR. KILPATRICK: I should perhaps explain why the question arose. I'm thinking in terms of perhaps designing something like a case controlled study going from

cases back to see what the risk factors were and whether thalidomide is involved because we've heard that other prospective studies may not be determining of whether thalidomide causes fetal effects. But I thank you for that.

The second question is concerned with transmission. The general public has been alerted to the transmission of HIV in a variety of ways, in fact perhaps overly sensitized to it. I've been struck by the fact that thalidomide is excreted in urine. Is it excreted in saliva? We've heard about it's unknown as to whether sperm contains thalidomide, and breast milk is uncertain. Can you make any observations about the accidental transmission of thalidomide to childbearing women?

DR. MOORE: I cannot. I don't know if anyone from Celgene --

DR. McGUIRE: Dr. Bashaw had a question. Maybe he also can help answer one of your questions.

DR. BASHAW: Actually it was a comment regarding the time that thalidomide would remain in the body. It's sort of another way to look at it. We looked at the solubility of thalidomide looking for oral solutions, and in water has a very poor water solubility, but its alcohol solubility is equally almost as poor. It has really got a unique solubility profile. About the best

thing it's soluble in is only DMSO which sort of incorporates both polar and nonpolar solubilities.

So, in terms of would thalidomide itself readily go into fat tissues, based on its chemical nature, most likely it would not, and when you look at the hydrolysis products, again the structures that I presented in my review, the theoretical ones for metabolites, again, they all contain carbonyls and carboxylic acid groups which would put it more to the polar side where it would be in the body water.

Although it's not a definitive answer, I don't think you'd have the same magnitude problem as you have with Psoriatain or acitretin or the isotretinoins. Nothing like that. There may be some deposition, but I don't believe it's very major based on the solubility information we have right now.

DR. McGUIRE: Dennis, can you speak to excretion in milk or presence in semen, saliva?

DR. BASHAW: I can only speculate. We have not collected any data on it. It's probably secreted in saliva. As for breast milk, as for semen, because of the protein contents there and their fat makeup, especially in breast milk, I really would not want to comment with any degree of certainty on those. Like I said, its solubility is rather unusual. It potentially could get ion trapped,

but I really wouldn't want to speculate beyond that.

DR. McGUIRE: But it could be measured.

DR. BASHAW: Yes. Oh, it certainly could be. The analytical methodology I believe exists.

DR. McGUIRE: Are there other questions for Dr. Moore? Yes, Dr. Orkin.

DR. ORKIN: It's interesting that Dr. Moore suggested that there may be some other abnormalities later on in the pregnancy that are not typical of thalidomide as we recognize it.

Along that line, I thought that Mr. Warren's comment about the fact that the second generation in the mothers is not known. I wonder is there any data -- and I think the answer is probably no, but it would still be interesting to know, important to know if there were other children of those mothers who had some abnormalities that were not of the typical form but were atypical.

DR. McGUIRE: In November, Dr. Lammer had a lot of information concerning the etretinate children.

Mr. Warren, did you have a comment?

MR. WARREN: I actually had a question because you brought up an interesting point, a speculation for us. When we were evaluated as thalidomiders -- that's what we call ourselves -- way back then, we could pinpoint to the day when our mothers had ingested the drug. From

standpoint from all of our information, those that survived are a result of the first trimester in this highly sensitive period, but we've always suspected that it was possible that it would be at least into the early second trimester or possibly throughout the pregnancy. I'd be really curious if anybody had any information about that.

DR. MOORE: Well, I'm not the first person surely to suggest that there could be other problems in addition to structural birth defects. But in order for the structural birth defects to occur, that exposure would be early in the first trimester during organogenesis, but I really can't speculate. I think it's an unknown to us if anything later in pregnancy occurs.

MR. WARREN: I just wanted to follow up on that because we've always believed that there were perhaps other thalidomiders born that may have been smaller babies because maybe it was during the growth process or with other not necessarily phocomelic disabilities, that people had not recognized that their disabilities could have been a result of thalidomide, just to qualify my question, because nobody really knows. Those of us that manifested the physical disability were pretty much pronounced thalidomiders. It was a gray area, so the rest of the population who may have had disabled children at that time, we may never be aware of whether there are more

thalidomiders out there than we're currently aware of now.

DR. MOORE: There are multiple outcomes that can be looked at, including birth weight, growth, the functional parameters I was talking about, even whether or not there's an excess of fetal death, and all those reproductive outcomes can be looked at with different exposures. But I'm not aware of really good data on this for thalidomide.

DR. McGUIRE: Dr. Simmons-O'Brien has a question.

DR. SIMMONS-O'BRIEN: Well, actually it's a comment. Having reviewed a significant portion of the literature on thalidomide, I believe -- and I'm not certain if Dr. Holmes is still here, but I believe he's an author on a paper that is a very nice paper talking about what have we learned from the embryopathy.

Geneticists have gone back and have looked at the cases, some of the cases in Europe and here in the United States, and have shown that the actual syndrome goes far beyond phocomelia. There are children who were born without ears, anotia. I believe that actually might have been the first retrospective case of a worker who worked in the Gruenenthal plant who gave thalidomide to his pregnant wife and had a daughter who was born without ears. So, the actual syndrome can encompass many clinical presentations,

pelvic girdle abnormalities.

But in the same breath, the paper also stated that there are numerous medications that are also used that can cause similar type of defects, as well as some later discovered genetic syndromes, and Holt-Oram being one of them by Victor McCusik. So, in the literature this is discussed.

DR. MOORE: I agree with you completely. There are several authors and teratologists who have gone back and discussed that. It's a reality in birth defects that a complete evaluation is needed of a child who has structural birth defects before a cause is placed on that occurrence.

DR. McGUIRE: Dr. Moore, thank you. I think we'll go on to the last presentation.

DR. MOORE: Thank you.

DR. McGUIRE: Colin Crawford will speak on thalidomide neurotoxicity which, by the way, was a subject dealt with in some detail at our November meeting.

DR. CRAWFORD: Thank you very much for asking me to talk. I'm Colin Crawford. I trained in New Zealand and then I came to the U.K. to do postgraduate work, and then in 1966 I went to Africa to work with leprosy patients, both clinical management and field work, firstly in northern Nigeria and then in Tanzania. So, I had about four and a half years of experience with leprosy patients.

Now, thalidomide neuropathy is a very serious complication that can lead to severe sensory loss which may be irreversible. In fact, two British pharmacologists, Darcy and Griffin, have stated, referring to the events of 1960 and 1961, that this side effect alone was severe enough to cause the demise of the drug, even if the teratogenic disaster had not supervened.

The teratogenic effects can be avoided by not giving the drug to women of reproductive age, but anybody who takes the drug is liable to develop a neuropathy.

If we can have the first slide please. We can look at the clinical features. It's initially a sensory neuropathy. All modalities can be affected, but an important point is there may be a selective loss of superficial pain and temperatures which can be confused with leprous neuropathy.

The dying-back neuropathy which means the main involvement is in the distal extremities of the lower limbs, symmetrical nature, and common symptoms are burning pain in the feet and cramp-like pains in the calf. The knee and ankle reflexes may be diminished, but if there's pyramidal tract involvement, they may be increased with extensive plantar responses. As a late stage, if the drug is continued, there is a characteristic paralysis of the proximal muscles.

The pathology is it's an axonal neuropathy first affecting sensory myelinated fibers, can be detected by sural nerve biopsy, and unmyelinated fibers appear to be unaffected.

You can see on the right here the normal control of vesicular sural nerve biopsy and the great loss of myelinated fibers in a patient who has taken thalidomide.

The control values show that there's a bimodal distribution, with the larger diameter fibers in the 10 to 20 micron range. In these 2 patients who have been given thalidomide, there is a great loss of myelinated fibers, and in some cases a shift to the left, implying some degree of regeneration of smaller caliber fibers.

The third measure to detect the neuropathy -- you may not be able to read this too well. It's an axonal neuropathy, so the most sensitive test is sensory nerve action potentials, and nerve conduction studies are usually normal.

In this French study, which was published in 1986, for non-leprosy disorders, mainly dermatological, the control values are 16 here and the sural nerve action potential was grossly diminished in many patients. Some were normal. These were the symptoms that the patient got.

On the right here is the cumulative dose given

over several months. You can see 1 patient developed a neuropathy after only 9 grams. That would be 100 milligrams over 3 months.

Now, other features of the drug. The frequency in non-leprosy disorders is reported as at least 21 percent if sensory nerve action potentials are carried out to detect subclinical neuropathy.

There is no minimum dose below which it is safe to give the drug.

It's not due to hypersensitivity.

One study on the genetic factors did not seem to be significant.

Although these things may be significant, the latest papers suggest they may not be able to predict a neuropathy.

Really, in conclusion, the chances of developing a neuropathy are probably unpredictable.

The prognosis. If the drug is stopped, motor and pyramidal involvement is reversible. However, the sensory loss is permanent in 50 percent of the patients, even years after stopping the drug.

One of the things Dr. LaQuesne pointed out is this persistent painful paraesthesiae which were painful and disabling and were the most distressing thing about the effect of the drug.

Now, when we come to leprosy -- and you've heard about the literature -- neither or any of the clinical, pathological, or electrophysiological studies have been carried out in leprosy patients with erythema nodosum.

That's not a very good picture, but you've seen one before. The erythema nodosum, or ENL, painful nodules under the skin. They're generalized.

I think an important point that Dr. Wilkin made is that we should consider the skin manifestations, and I would add to that the rise in temperature which these patients have. There have been a lot of comments on the orchitis, the iritis, the arthritis, the nephritis, the amyloidosis, but personally I did not have the facilities to observe all these things. But certainly they're not, from a quantitative point of view, sufficient to run clinical trials and to test the efficacy of thalidomide.

Now, my own experience with patients with ENL, 14 patients: 7 in northern Nigeria and 7 in Tanzania. The important point is that on clinical neurological examination, 10 had no clinical signs of sensory loss due to the leprosy. Therefore, by giving thalidomide, it is possible to inflict permanent nerve damage on a leprosy patient who would have not developed this as a result of the disease.

4 of these had sensory loss. 2 were severe. One had a trophic ulcer, another had mutilation of the extremities.

Now, when we compare thalidomide and leprous neuropathy, there are similarities, as I've pointed out. In thalidomide, the sensory loss may be confined to superficial sensory modalities, and the distribution may be similar, being mainly distal and shading off proximally.

Differences are the burning pain in the feet, which I had not observed and it's not recorded in the literature, or cramp-like pains in the calf in 16 out of 22 patients, not present there.

Some patients may develop ataxia with thalidomide. It's not present in there.

The reflexes are always preserved in leprous neuropathy, but there may be loss but in under 50 percent.

Then if the drug is continued, distinctive proximal muscle paralysis which is not present in leprosy.

So, the most important observation is the clinical neurological examination before thalidomide is administered, and we have no details of patients with ENL of what that is. And any deterioration over weeks or months must be due to the drug. Sensory loss from lepromatous leprosy is very insidious and unlikely to occur over a short period. We know that from Hansen's original

observation of the natural history of the disease.

Now, there have been various reasons why thalidomide neuropathy has not been reported in cases with ENL, and as you've heard, it's either none has been reported or only less than 1 percent. One of the reasons comes from Waters, that the nerves of lepromatous patients are relatively insusceptible to thalidomide-induced nerve damage. This is based on the preservation of reflexes in leprosy patients who have received thalidomide. However, they were only absent in under 50 percent from Fullerton's study. They will be retained if there's pyramidal tract involvement. In a review article of the original thalidomide neuropathy, they weren't regarded as a useful diagnostic sign.

And the reflexes were preserved in a patient with AIDS who developed a neuropathy after taking thalidomide, and the nerve biopsy in that patient showed -- here's the normal control -- there's a gross loss of myelinated fibers in this patient.

Another reason put forward by Robert Hastings, who had never seen a case of neuropathy, this could be the disease has already -- we have no data as to what the precise clinical examination there was. As I've said, in my patients, 10 out of 14 didn't have clinical neurological abnormalities. It's published in the Journal of

American --

And electrophysiological studies have been taking place. In this recent editorial from the Lancet, the agent has been used in leprosy for many years, but leprosy patients treated with the drug even after careful study -- and this is a reference to a letter published in 1969 which is on the motor conduction velocities in the ulnar nerve at the elbow. While thalidomide neuropathy is an axonal neuropathy, conduction studies will not be affected.

Thalidomide neuropathy is a dying-back neuropathy, so the main and severe involvement will be in the distal parts of the lower limb.

As it's mainly sensory, the motor conduction velocities are unlikely to be affected.

This study was carried out in 1969 only four years after the drug was administered. We have had nearly another 25 years to assess whether there are side effects.

Now, recently the United Kingdom have laid down guidelines for the administration of thalidomide to patients in Britain. Each patient is provided with an information sheet, and on it is stated in bold letters, "should you develop pins and needles, you must stop thalidomide immediately." They point out in the guidelines and in an accompanying article it was a common, severe, and

often irreversible side effect of treatment with thalidomide.

They recommend at least one, preferably two, pretreatment measurements of sensory nerve action potentials in at least three nerves -- sural, median, and the ulnar nerve -- and that they should be repeated at 10 gram increment in total dose or at six monthly intervals, whichever is the smaller. A fall from the baseline of greater than 40 percent should be regarded as significant and the drug should be stopped. If this is done, the hope is that the symptoms may -- that they may offer the best hope of recovery.

However, if we go back to the French -- and on the labeling, the label should contain a warning, "contains thalidomide."

Now, some of you may have been the film brought out by the ITV First Tuesday on the teratogenic disaster in Brazil. Up till that point, the bottles containing thalidomide were administered to patients in the U.K. without the warning "contains thalidomide." It was only after the film was shown that that was recommended.

On the labeling, it causes serious damage to babies if taken by women during pregnancy.

However, there's no warning about risk of nerve damage, and the U.K. law states that suppliers of a drug

are not legally required to provide contraindications, warnings, and precautions. It is the responsibility of the medical person giving the drug to explain to the patient.

If we go back to the electrophysiological studies, this number 4 and number 9 are asterisked. These were patients who developed a neuropathy with a fall in the sural nerve action potential, and the drug was stopped. However, there were no recovery by symptoms a year after stopping the drug and the electrophysiological abnormalities persisted. So, even under the optimal or semi-optimal conditions, it has been impossible in those two cases to prevent a neuropathy from occurring.

Now, I was so concerned several years ago about the fact that the patients may not be warned and the risk because Dr. Jacobson in a review article in this journal, The Star -- the Star was published by Stanley Stein, a famous Hansen's disease patient because he thought that the patients with Hansen's disease should have their own view and they should be able to publish their own journal. Dr. Jacobson wrote an article in which he did not mention the neuropathic side effects.

I should state that most of the textbooks in America and in the U.K. of physicians who are writing about the treatment of ENL do not mention the neuropathy as a side effect. I'm talking about Harrison's Internal

Medicine, 1997, the Sissel's book, William Kelly's book, and Mandel's Infectious Disease book. None of these people mention neuropathy as a side effect.

So, much of what I've said to you was published in this article. This is just a summary, but it did not meet with the approval of the physicians.

So, in conclusion, thalidomide neuropathy has not been excluded in patients for ENL. The guidelines to detect thalidomide -- clinical, pathological, electrophysiological -- have not been utilized in leprosy patients.

And even if the U.K. guidelines were adopted in patients with ENL, thalidomide could not really be used because of the frequency of sensory disturbances. Although some may not have a neuropathy, they have thickened nerves. They'll bang their arms and their legs. They'll develop paresthesia. So, it would be very difficult to use the drug.

The lack of knowledge of the fundamental pathological, electrophysical changes in patients with this complication of leprosy would make interpretation very difficult.

Thank you.

DR. McGUIRE: Thank you, Dr. Crawford.

We have time for questions. Dr. Bergfeld.

DR. BERGFELD: I have a question, Doctor. I was wondering if you infer here that 100 percent of those patients who were treated in the U.K. with thalidomide got a peripheral neuropathy. Is that your inference here?

DR. CRAWFORD: No, no. I don't know what the figures for neuropathy are in the U.K. I don't think they've been published.

DR. BERGFELD: It was my impression it was about 6 percent. Is that too low?

DR. CRAWFORD: Well, I think the French study shows 21 percent at least. There's another study by Harland. I think you're right about that, that it went up to 50 percent in a small number of cases. Yes, I think it could be as high as 50 percent.

DR. SIMMONS-O'BRIEN: Dr. Crawford, with your experience in your particular patients, could you comment a little bit on their dosages and how long they took those doses. In at least the patients who did get the neuropathy, did that in any way correlate with the amount of drug and the length of time that it was given?

DR. CRAWFORD: In my patients?

DR. SIMMONS-O'BRIEN: The patients from Tanzania --

DR. CRAWFORD: No, I think there have been various conclusions drawn, that the cumulative, the total

dose was important and the daily dose might be, but the paper from Harland referred to suggests these may not be significant features. But I don't know what the up-to-date picture is. There's certainly no minimum dose below which it's safe to give the drug.

DR. McGUIRE: No more axonopathy questions.

DR. KILPATRICK: If you want me to ask a question, I can ask a question.

DR. McGUIRE: I'm pretty enthusiastic about it, yes.

DR. KILPATRICK: Sir, in the United Kingdom I notice that you use the word "thalidomide" in your labeling. Was that deliberate or was that in avoidance of a trade name or was that how it's known there?

DR. CRAWFORD: No. It is known as thalidomide. The original name was Distaval back in the 1960s when the drug came back. But as I tried to point out, up till the time of the film which was shown, the bottle just contained GC233 or something like that, and it was the director of the film, James Cutler, who pointed that out. I might say the committee didn't give him credit for bringing that to light.

DR. McGUIRE: Dr. Cornblath, do you have any comments?

DR. CORNBLATH: I think in general we both

looked at the same literature and come to the same conclusion. It would be nice to have some modern day prospective studies in these populations that clearly prospectively doing electrodiagnostic studies on people who are going to receive will prevent people from getting any neuropathy, that electrodiagnostic studies will pick up people before they have symptoms.

The only curious comment that I'd make here about your own personal experience is I was surprised to see that the 4 patients who developed neuropathy that you thought was from thalidomide actually developed what we would consider neuropathy of small fibers with mutilating acropathy and trophic ulcers, something that we don't usually associate with large fiber abnormality because you've shown, as have others, that the large fibers are abnormal and the small fibers are normal. So, it's surprising that you concluded, to me at least, that the neuropathy in those 4 patients was due to their thalidomide when that was a small fiber abnormality and not a large fiber abnormality.

DR. CRAWFORD: Yes. I should have made the point clear. I had never used thalidomide in my patients, and those observations were made on the leprous neuropathy.

DR. McGUIRE: Well, while both of you are still here, I really need some help on this point. The sparing

of the Hansen's population from the peripheral neuropathy. Do you think that was an artifact of finding a signal and a lot of noise or do you think there really is some sparing of that population?

DR. CORNBLATH: I would agree with Dr. Crawford. One of the primary problems is that the electrodiagnostic studies that have been done would not pick up the neuropathy that might occur in this population. So, what we're left with, if we look at the literature alone I believe, is clinical opinions about whether the patients with ENL who take thalidomide develop these typical distal symptoms in their feet. At least based on the literature that I read and responses in particular to a series of letters that were written I think in the Lancet several years ago, experienced leprologists state they don't see people taking thalidomide with leprosy who develop these typical symptoms in the feet.

Granted, electrodiagnostic studies haven't been done, but at least based on clinical data, which is I think the best we have, I can't see that there's good evidence either in the literature or by these people's experience that the patients do. Maybe some of the other leprologists who treat these patients long term could comment.

DR. CRAWFORD: Well, as I said, I think one of the problems -- and we've heard from Dr. Yoder about the

current approach to leprosy is mainly a dermatological one based on the current classification, and there's no requirement really to conduct a clinical neurological examination. I think that's something which possibly is necessary to get baseline data.

DR. McGUIRE: Dr. Miller, you have a question.

DR. MILLER: Dr. Crawford, you said that you did not use thalidomide in your patients?

DR. CRAWFORD: No.

DR. MILLER: How did you treat ENL and what kind of results did you get?

DR. CRAWFORD: In those days, we used to lower the dose of dapsone. We had dapsone monotherapy and then in Tanzania we had clofazimine. My opinion is -- and there was current opinion -- that low doses of dapsone diminish the severity of the ENL and you didn't get ulceration. Provided you kept the morphological index down, being the percentage of viable bacteria, the patients did fairly well because ENL is not bacteriologically active. I mean, there's dead bacteria but they're not active. So, if you can maintain that, then I think they do quite well.

Some needed small doses of prednisone, 10 milligrams a day.

But in no sense was this a controlled clinical trial. It was just working experience which one used among

the leprosy people in northern Nigeria. This is the way I learnt to do it and this I found satisfactory.

I wasn't asked to talk about alternative management. I think it's worth making the point. With clofazimine, the pigmentary side effect is important. However, there have been developed non-pigmentary derivatives of clofazimine, which one would hope may be useful as substitutes for clofazimine.

DR. McGUIRE: Would you like to comment?

DR. GELBER: Yes, I would.

Dr. Crawford, I just want to assure you -- I'm Bob Gelber and I've treated leprosy patients in this country for quite a while, most notably between 1979 and 1984 where in San Francisco I was taking care of about a quarter of the U.S. patients. I think Dr. Rea has another quarter of the patients.

We routinely in our center and in all of the centers in the United States, on an initial basis and on an annual basis, do detailed sensory testing, motor strength testing using initially von Tri's hairs but now these monofilaments. So, we are actually looking very closely at our patients. Most of us are quite aware that the serious complications of leprosy are neurologic and not dermatologic.

I might say that in my experience, I never see

any major changes in those hair sensations, nor do I get an awful lot of patients that complain of increasing numbness or severe paresthesias. But those kinds of things are often very hard to tell clinically from progressive leprous disease which may be not either reaction or bacteriological failure but even well-treated patients who do not have bacteriological failure may have minimal deterioration.

But the bottom line here is that, number one, we are alert to this. We do follow this and we don't see it.

DR. McGUIRE: Yes, please. Dr. Yoder.

DR. YODER: I would like to reaffirm, first of all, what Dr. Gelber just said about monitoring Hansen's disease patients. All patients who come to our center have very detailed neurological exams and occupational therapy and physical therapy with the monofilaments 100 percent, and that is the standard of care in the United States in our centers. Many of these testings are done by nurses in other centers where they don't have the occupational and physical therapists that we have.

We do use nerve conduction studies as well in problem cases and situations where we feel we need that other evaluation.

The other comment I would make about the severity of the disease and I alluded to that this morning.

I have worked in Africa also in several countries, and my experience was that ENL actually often was a milder situation there than it is in the United States. In Carville my experience is that we don't often see the milder kind of cases that we did see in Africa where you could use small doses of prednisone or even simple analgesics. That's rare in my experience. Very few of the cases we see at Carville, if we did not use thalidomide, we would have to use significant doses of prednisone. Clofazimine would be quite inadequate because these people are ill with fever, pain, diffuse rash, and require something more than simple, very mild intervention.

DR. McGUIRE: Thank you very much.

DR. CRAWFORD: I think it's really a mystery why you get frequencies of 21 to 50 percent and not in leprosy.

But the other point I think is that sensory nerve action potentials, to my knowledge, haven't been done, and this, being an axonal neuropathy, is the most critical test.

If the U.K. guidelines are considered and this is what they recommend, this is going to prove extremely difficult in leprosy patients because we have no baseline information about what sensory nerve action potentials are in patients with ENL and how you monitor them.

DR. McGUIRE: Mr. Warren.

MR. WARREN: I actually appreciate being a part of the topic. We've always been concerned ourselves that we thought that there should be a lot more warnings regarding the potential for nerve damage and neuropathy.

But my question is -- because we are concerned also about the off-loading, if you will, off-labeling, my concern is then, from what I'm understanding here, in Great Britain they're not warning regarding nerve damage or any potential for neuropathy on the labeling or in any of their literature? Is that true?

DR. CRAWFORD: No. They are well aware of the neuropathy. It's just an anomaly about U.K. law that it's not a responsibility of the manufacturer to mention it in the labeling. According to the chairman of the Committee on the Safety of Medicines, the law would have to be changed. I think that's wrong, but one would hope that with all the trouble, that the manufacturer would volunteer to mention the side effects.

MR. WARREN: So, who does it fall to? Is it the doctor's responsibility then before prescribing, and is that carried through? Do you have any -- I just feel like there's a piece missing.

DR. CRAWFORD: We don't know what their position is. I don't treat any patients in the U.K., so I

don't know what their attitude is.

DR. McGUIRE: Dr. Crawford, I'm about ready to make a few closing announcements. Thank you very much.

I'd like to thank the people who spoke in the public discussion, and I'd like to thank the members of the agency and the sponsor for your precise and clear explanations of what we're here about.

This room will be locked tonight if any members of the committee wish to leave their books here.

I request that all of you take your questions home with you this evening and have a look at them. It will make tomorrow go a little easier.

I think that's about it for me, and the Executive Secretary has some remarks.

MS. RILEY: Thank you. This is for the members only. There is an address verification sheet in your folder. If it could be filled out and returned to me by sometime tomorrow, that would be great. There's an item missing, though. If you have an e-mail address, I would really appreciate you adding that to the list. Thank you.

DR. McGUIRE: We are adjourned and will convene in this room at 8:30 tomorrow morning.

(Whereupon, at 5:00 p.m., the committee was recessed, to reconvene at 8:30 a.m., Friday, September 5, 1997.)