

CENTER FOR DRUG EVALUATION AND RESEARCH
FOOD AND DRUG ADMINISTRATION

FORTY-SEVENTH MEETING
OF THE
DERMATOLOGIC AND OPHTHALMIC DRUGS ADVISORY COMMITTEE

2015
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8:36 a.m.
Thursday, September 4, 1997

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Holiday Inn
8120 Wisconsin Avenue
Bethesda, Maryland

CELGENE EXHIBIT 2022
Coalition for Affordable Drugs VI LLC (Petitioner) v. Celgene Corporation (Patent Owner)
Case IPR2015-01096

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P R O C E E D I N G S

(8:36 a.m.)

1
2
3 DR. McGUIRE: This is the 47th convening of the
4 Dermatologic and Ophthalmic Drugs Advisory Committee
5 meeting of the Food and Drug Administration.

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

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

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

16 The following announcement addresses the issue
17 of conflict of interest with regard to this meeting, and is
18 made a part of the record to preclude even the appearance
19 of such at this meeting.

20 Based on the submitted agenda and information
21 provided by the participants, the agency has determined
22 that all reported interests in firms regulated by the
23 Center for Drug Evaluation and Research present no
24 potential for conflict of interest at this meeting.

25 With respect to FDA's invited guest speaker,

1 Mr. Randolph Warren, he has reported interests which we
2 believe should be made public to allow the participants to
3 objectively evaluate his comments. Mr. Warren would like
4 to disclose that he has, on two occasions, discussed
5 Synovir, thalidomide, with the Celgene Corporation.

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

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

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

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

23 Thank you.

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

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

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

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

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

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

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

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

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

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

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

23 | DR. MCGUIRE: I am Joe McGuire, from Stanford
24 | University, dermatology and pediatrics.

25 | MS. RILEY: I am Tracy Riley, the Executive

1 Secretary to the committee.

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

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

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

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

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

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

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

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

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

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

1 DR. MCGUIRE: Thank you very much.

2 The first remarks will be presented by Mary
3 Pendergast.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 forward to hearing your deliberations.

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

6 DR. MCGUIRE: Thank you, Ms. Pendergast.

7 Dr. Weintraub.

8 DR. WEINTRAUB: Thank you, Dr. McGuire.

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

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

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

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

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

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

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

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

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

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

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

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

25 Thank you.

1 DR. MCGUIRE: Thank you, Dr. Weintraub.

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

4 DR. WEINTRAUB: That is correct.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

25 | Thank you.

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

2 DR. McGUIRE: Thank you, Ms. Riley.

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

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

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

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

1 (Applause.)

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

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

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

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

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

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

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

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

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

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

1 Thank you.

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

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

6 (Pause.)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 | thalidomide into healthy human volunteer studies actually
2 | later this month.

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

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

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

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

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

3 Could I have the first slide, please?

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

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

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

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

1 look at the metabolism of thalidomide.

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

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

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

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

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

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

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

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

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

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

6 We looked at a series of cytochrome P450
7 isozymes, and in no case was there any evidence of
8 inhibition or induction for CYP 1A2, 2A6, 2B6, 2C9, 2C19,
9 2D6, 2E1, and 3A4. And these are the enzymes that are most
10 commonly associated with drug metabolism. So, we don't
11 anticipate that there will be any impact of thalidomide on
12 other drugs or any effect of other drugs on the metabolism
13 of thalidomide.

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

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

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

3 Looking in healthy volunteers at the 50- to
4 400-milligram dose range, there is dose proportionality
5 with respect to the area under the curve. In fact, the
6 extent of absorption is the same from 50 to 400 milligrams.
7 However, Cmax does not increase proportionally due to
8 delayed absorption or prolonged absorption between the 200-
9 and 400-milligram dose. How that evidences itself is,
10 again, the apparent elimination half-life, which we believe
11 is truly the absorption half-life, changes from 5.5 to 7.3
12 hours between 200 and 400 milligrams.

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

22 The other observation was that absorption and
23 elimination half-lives were somewhat longer at this
24 400-milligram dose.

25 Taking this to the next step, they are similar,

1 as we stated before. And the absorption half-lives were
2 somewhat longer, but the metabolism that we observed in
3 vivo is essentially confirmed in this 400-milligram dose
4 study in Hansen's disease patients. In fact, the three
5 metabolites that would be anticipated to be formed were not
6 observed in the plasma of these subjects. Less than 1
7 percent of the dose was excreted intact in urine, and even
8 a lesser extent, less than .1 percent of the dose, was
9 excreted by one of the hydroxy metabolites,
10 4-hydroxy-thalidomide.

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

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

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

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

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

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

11 | Also, supporting the single-dose study at the
12 | 400-milligram dose, the purported metabolites, again, were
13 | not measurable in plasma, and only less than 1 percent of
14 | the daily dose was excreted in urine. And only
15 | approximately 0.2 percent of the dose was found in urine as
16 | the 4-hydroxy metabolite. Neither of the other two
17 | metabolites that we looked for were observed.

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

25 | In addition, when a single two-tablet dose of

1 Ortho Novum oral contraceptive was administered, the
2 pharmacokinetics of the ethinyl estradiol and the
3 norethindrone from that product was not altered by the
4 21-day administration of thalidomide.

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

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

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

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

23 Secondly, gender. Female subjects composed
24 26 of the 83 subjects that were studied during these
25 clinical trials. Both females and males exhibited very

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

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

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

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

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

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

1 | will do it either way.

2 | DR. MCGUIRE: Does the committee have any
3 | questions at this point?

4 | Dr. Bergfeld.

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

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

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

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

1 DR. BERGFELD: You have not measured the fat?

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

6 DR. McGUIRE: Dr. Shannon?

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

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

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

22 DR. COLBURN: You can't.

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

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

4 DR. MCGUIRE: I think that is all for the
5 committee right now.

6 DR. THOMAS: Okay. Thanks again, Wayne.

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

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

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

25 Leprosy is an infectious disease primarily of

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

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

16 In the United States, we estimate approximately
17 7,000 or so cases that have been diagnosed and treated for
18 the disease. Not all of these are now currently under
19 treatment or have active disease, but these are on
20 registers.

21 However, probably the more important numbers to
22 look at what's ahead for this disease is to look at the new
23 case rates, or incidence rates. In the U.S., approximately
24 200 new cases occur per year, or are reported per year.
25 This has been fairly consistent. It is down slightly, but

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

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

11 | So, in spite of the fact that WHO is talking
12 | about elimination as a public health problem by the year
13 | 2000, they are not reflecting the real new cases numbers,
14 | which are staying almost constant or decreasing very
15 | slightly. So, this disease is going to be with us for many
16 | years to come.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 and generally are tender.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 way to manage these patients.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

7 DR. MCGUIRE: Thank you, Dr. Yoder.

8 Are there questions from the committee? Yes.

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

14 DR. YODER: Well, the proportion of males to
15 females with leprosy overall is something in the order
16 60/40. You know, there are more males than females.

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

23 DR. MCGUIRE: Dr. Hashimoto.

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

1 zero.

2 DR. YODER: Yes.

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

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

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

24 DR. McGUIRE: Dr. Orkin.

25 DR. ORKIN: Is the pigmentation with

1 | clofazimine persistent, continuous, permanent?

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

5 | DR. MCGUIRE: Dr. Crawford.

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

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

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

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

1 Is that what you were asking?

2 DR. CRAWFORD: Yes.

3 DR. YODER: Yes.

4 DR. MCGUIRE: Dr. Shannon?

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

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

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

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

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

10 | DR. MCGUIRE: Dr. Simmons-O'Brien.

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

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

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

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

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

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

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

20 | DR. MCGUIRE: Dr. Duvic has the next question.

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

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

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

5 | DR. YODER: I missed your last numbers.

6 | DR. CRAWFORD: Fifty-three.

7 | DR. YODER: Of what?

8 | DR. CRAWFORD: New cases of leprosy. That is
9 | the mortality and morbidity report for July the 18th. That
10 | is the latest figure we have in the U.K. And last year,
11 | 112 new cases.

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

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

18 | DR. CRAWFORD: Yes.

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

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

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

1 DR. MCGUIRE: Okay.

2 Yes.

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

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

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

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

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

20 DR. DUVIC: Okay.

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

25 (Applause.)

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

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

15 DR. MCGUIRE: Dr. Moore.

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

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

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

1 infectious disease --

2 DR. YODER: You are from?

3 DR. MOORE: The CDC.

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

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

17 You had another question I think.

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

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

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

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

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

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

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

23 DR. MCGUIRE: This is ENL, not new cases of
24 leprosy.

25 DR. YODER: This is patients that are on

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

3 DR. McGUIRE: Thank you.

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

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

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

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

18 DR. ZELDIS: Thanks, Steve.

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

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

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

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

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

20 Let me get to the first slide.

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

1 information -- at least a global overview -- of how over
2 4,700 patients have fared with the drug.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 | protocol.

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

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

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

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

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

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

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

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

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

25 At baseline, all subjects had fever and all

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 | What happened to these 5 people who were,
23 | quote, treatment failures, because they took acetaminophen
24 | 4 days into the protocol. Now, at this point, they were
25 | off paracetamol or acetaminophen. And as you can see, it

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

23 Basically, each year Carville collected between
24 227 to 341 case report forms, for a total of 4,767 case
25 report forms collected between 1978 and 1994. In the

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

4 | This translated into 33 to 234 new patients
5 | initiated each year, for a total in this experience, over
6 | 17 years, of 1,367 patients who received the drug.

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

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

17 | 85 percent of the patients had lepromatous
18 | leprosy. About 15 had borderline leprosy. And the average
19 | patient had the Hansen's disease for at least 5 years.

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

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

6 How did these patients do?

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

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

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

25 Furthermore, some treatment failures -- about

1 half -- with continued therapy, became responders.

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

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

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

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

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

1 abstracted the data.

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

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

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

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

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

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

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

11 Equally important, 8 placebo-treated patients
12 who failed therapy were subsequently treated with
13 thalidomide, and all of them, 100 percent, responded within
14 4 to 11 days. Furthermore, when patients had relapses off
15 thalidomide and they were placed on thalidomide, the
16 majority of these episodes did respond to repeat therapy.

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

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

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

10 Thalidomide also was deemed to be steroid-
11 sparing.

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

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

19 Thalidomide also was superior to
20 chloramphenicol.

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

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

1 | by reading this literature was progressive clinical
2 | improvement in 48 to 72 hours, including the loss of fever
3 | and painful skin lesions. All studies found greater than
4 | 90 percent response. This is very repetitious. I'm sorry,
5 | but that is the literature.

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

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

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

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

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

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

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

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

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

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

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

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

8 The most frequent adverse events that we noted,
9 that are noted in ENL trials, are sedation, rash, and
10 constipation. While peripheral neuropathy can occur, it is
11 an infrequent occurrence -- usually occurring in less than
12 1 percent of patients with ENL. Furthermore, no
13 drug-related serious or adverse events have been described
14 in the ENL studies and the published literature. And that
15 is quite a strong statement, but I am going to show you the
16 database, which is quite large.

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

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

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

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

13 Of the ENL trials, we have data on 23. If you
14 look at the non-ENL trials, for all the other indications,
15 we are talking about over 2,200 patient exposures, of which
16 231 are in HIV trials conducted by Celgene, and 671 for
17 other indications on physician INDs, emergency INDs, and
18 other small trials which Celgene is conducting. And then,
19 the published literature, which is composed of 93 studies
20 from which we could glean safety information on 1,315
21 additional patients.

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

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

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

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

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

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

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

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

1 studies.

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

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

17 When we looked at E-001, which is a U.S. ENL
18 study, which has recruited 6 patients so far, 5 of the 6
19 had AE's. Again, none severe. The most common AE's were
20 fatigue or asthenia, arthralgias in 2, fevers and chills in
21 2.

22 When we looked at the Carville experience,
23 1,387 subjects evaluated over a 17-year period, 279, or 20
24 percent of the people, had adverse events. Approximately
25 half of them had more than one adverse event. The most

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

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

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

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

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

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

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

13 | In the published literature, there is no case
14 | of neurotoxicity mentioned. And in the Carville
15 | experience, there were 18 episodes described among the
16 | 1,387 patients. However, some of these episodes are
17 | redundant and occurred in the same patient.

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

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

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

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

10 In an open-label AIDS wasting trial involving
11 113 patients, the most common adverse events were
12 leukopenia, diarrhea, peripheral neuropathy, rash, fever,
13 pneumonia, and somnolence again.

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

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

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

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

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

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

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

25 Another study performed with our drug showed

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

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

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

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

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

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

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

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

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

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

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

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

3 | As far as laboratory abnormalities, we only
4 | really found one. And that is leukopenia or neutropenia,
5 | which, in the ENL studies, is between 0 to 8.4 percent, and
6 | in our non-ENL studies, in Celgene's studies, it is about
7 | 20 percent. In the Chemie Gruenenthal study, it was about
8 | one-third. And in the literature, it is about 2 percent.

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

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

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

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

1 | adverse events, followed very rarely by peripheral
2 | neuropathy.

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

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

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

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

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

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

1 ENL, to us higher doses.

2 Thank you very much for your patience and
3 consideration.

4 DR. MCGUIRE: Thank you, Dr. Zeldis.

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

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

13 Dr. Cornblath.

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

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

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

25 I just want to point out two things -- three

1 items from before, and bring you up to date.

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

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

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

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

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

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

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

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

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

16 | Thank you very much.

17 | DR. MCGUIRE: Thank you, Doctor. Will you be
18 | here after the break, Dr. Cornblath?

19 | DR. CORNBLATH: Yes.

20 | DR. MCGUIRE: Let's have a break until 11:30.

21 | (Recess.)

22 | DR. MCGUIRE: Could I invite the advisory
23 | committee to have a seat?

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

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

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

6 Dr. Williams.

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

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

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

1 positive evidence of universal compliance.

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

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

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

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

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

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

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

24 | That caused us to look at other programs.

25 | Novartis, previously Sandoz, introduced

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

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

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

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

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

1 Celgene would make that available.

2 A regimen of pregnancy testing for women with
3 childbearing potential.

4 Informed consent.

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

7 And, lastly, a mandatory outcomes registry
8 survey.

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

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

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

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

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

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

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

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

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

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

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

1 | that works at the pharmacy level in a moment.

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

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

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

1 | gynecologist who would be.

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

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

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

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

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

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

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

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

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

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

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

1 Thank you very much.

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

6 Dr. Bergfeld has a question.

7 Could we have the lights, please?

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

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

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

25 We believe that certainly any physician

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

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

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

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

1 MR. WILLIAMS: That is reasonable.

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

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

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

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

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

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

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

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

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

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

13 (Laughter.)

14 MR. WILLIAMS: A point well taken.

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

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

25 MR. WILLIAMS: Let me address managed care, as

1 best as I can, first.

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

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

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

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

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

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

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

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

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

4 DR. MCGUIRE: But the registry is an ENL
5 registry. Correct?

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

8 DR. MCGUIRE: Well, that is quite different.

9 MR. WILLIAMS: Yes.

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

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

22 DR. MCGUIRE: Dr. Mindel.

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

25 MR. WILLIAMS: The informed consent, as it is

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

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

7 | MR. WILLIAMS: That is correct.

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

10 | MR. WILLIAMS: That is correct.

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

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

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

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

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

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

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

22 | Do you want to add anything else, Bruce?

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

1 | today and from other sources.

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

11 | DR. MCGUIRE: Mr. Williams, thank you very
12 | much.

13 | MR. WILLIAMS: Thank you.

14 | DR. MCGUIRE: We have one more question for
15 | Mr. Williams?

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

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

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

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

5 | DR. MCGUIRE: Yes.

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

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

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

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

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

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

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

9 DR. MCGUIRE: Yes, this will be the last
10 question of the morning session.

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

13 DR. THOMAS: Absolutely.

14 DR. CRAWFORD: And what will it say?

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

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

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

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

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

8 Thank you very much.

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

(1:11 p.m.)

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2
3 DR. MCGUIRE: Good afternoon. I would
4 appreciate it if the participants and guests could be
5 seated. We have several oral presentations this afternoon.

6 Is Christopher Doyle here?

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

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

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

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

25 Rather, I am here in support of any and all

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 | I thank you again for the opportunity to
23 | address you today.

24 | DR. MCGUIRE: Thank you, Mr. Doyle.

25 | I invite you to stick around for a couple of

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

2 Is Dr. Holmes present?

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

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

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

10 Thank you.

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

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

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

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

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

10 | Thirdly, that she be on an effective
11 | contraceptive.

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

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

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

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

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

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

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

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

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

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

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

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

23 Thank you.

24 DR. McGUIRE: Thank you very much.

25 This advisory committee was addressed by

1 Dr. Lammer in November.

2 Is Lynn Klein here?

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

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

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

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

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

25 NORD is proud of its achievements, the

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

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

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

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

1 to do enormous harm as well as enormous good.

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

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

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

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

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

15 Thank you.

16 DR. MCGUIRE: Thank you, Ms. Klein.

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

20 Ms. Pearson.

21 MS. PEARSON: Thank you. I'm representing the
22 National Women's Health Network, a national consumer
23 organization. We are supported by membership dues from our
24 14,000 individual and 400 local organizational members. We
25 accept no financial support from manufacturers of

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1 | pharmaceutical drugs or medical devices.

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

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

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

1 organizations have to consider many layers of issues.

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

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

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

25 We also urge the FDA to concentrate on

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

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

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

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

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

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

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

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

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

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

25 But in what will probably be the most common

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

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

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

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

25 In conclusion, we would just like to say that

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

11 Thank you.

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

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

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

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

25 My name is Vicki Walton, and I am representing

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

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

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

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

25 | Treatment from Behcet's disease remains

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

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

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

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

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

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

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

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

12 | The first letter from my mother:

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

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

1 For two years, I was Vicki's primary caregiver
2 as she laid in bed, agonizing in pain. She was septic over
3 18 times, and withered away to near death until the miracle
4 of thalidomide was introduced into our lives. Within 10
5 months, Vicki was out of bed and out of her wheelchair,
6 taking care of herself. Most importantly, she was able to
7 enjoy the pleasures of being alive.

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

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

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

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

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

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

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

13 | Respectfully yours, Georgia Walton.

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

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

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

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

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

11 Thank you.

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

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

19 Ms. Cooper, thanks for your time.

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

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

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

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

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

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

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

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

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

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

22 | So, separate history from what is really a
23 | property of the molecule. We have other teratogens that
24 | have been approved after thalidomide came in the early
25 | 1960s, and we do not have the tragedies that have been

1 | reported for thalidomide.

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

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

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

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

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

1 keratinization. There are many, many dermatoses, maybe
2 3,000 separate dermatoses. We know that not all of them
3 are always going to have drugs approved for those
4 particular indications. And so there is going to be
5 off-label use. So, that happens with the drugs that we
6 have listed here.

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

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

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

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

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

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

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

1 cutaneous lesions of erythema nodosum leprosum.

2 Thank you.

3 DR. MCGUIRE: Yes. This is Dr. Kilpatrick.

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

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

16 DR. MCGUIRE: Yes, a question?

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

18 DR. MCGUIRE: This is Dr. Moore.

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

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

7 DR. MOORE: In humans?

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

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

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

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

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

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

6 | The mouse studies consisted of a single-dose; a
7 | 14-day repeat dose, where samples were taken on day 1 and
8 | 8; and a 90-day repeat dose study, where samples were taken
9 | on day 1 and 90.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

6 Thank you for your attention.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

11 | Here we have the dose proportionality data,
12 | again, referred to earlier. I think you can see pretty
13 | nicely that from 50 milligrams, 200 milligrams and 400
14 | milligrams, you do have dose proportionality. This was
15 | done in healthy volunteers, using a range of doses.
16 | Really, you are still seeing the same pattern of half-lives
17 | there that is very consistent. The half-life here is about
18 | 10 to 12 hours, I believe -- I'm sorry -- about 7 hours.

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

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

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

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

14 | Again, I think the message here is that if you
15 | are thinking of larger doses, there is going to be some
16 | limitation to what peak levels you can achieve. Again,
17 | that all sort of goes back to the question of what is
18 | important. Peak levels or area or sustained levels?
19 | Again, that is a question we really do not have a good
20 | handle on right now.

21 | This was a study we tried to look at metabolism
22 | of thalidomide. We did a study in patients with leprosy, 6
23 | patients, and we saw some interesting results. The red
24 | line that you see there is a subset of all the patients.
25 | The blue line, which shows a much higher plasma

1 concentration -- of course, this is a mean line -- is
2 somewhat higher.

3 In this study, there were 6 subjects, and 2 of
4 them were very different from the other ones. There was
5 really no real reason why. There is some suggestion that
6 they had more severe disease, but, then again, they were
7 all receiving the same dose, and there was not a real good
8 understanding as to why they did have these higher levels.

9 When they were taken out, clearly, when you
10 look at the comparison back to the old data from the
11 previous study, which is the green line, the red and green
12 lines do show some similarity, even with the other
13 patients. When one looks at the elimination rate, one sees
14 that they are very similar across all three groups.

15 What could this possibly be is hard to say.
16 Unfortunately, doing a very small study with 6 subjects, it
17 is hard to make hard and firm conclusions. There is also
18 the complicating factor that these 6 subjects were on a
19 total of 47 different medications, when you go through
20 their patient records. So, whether or not you are seeing
21 drug-drug interactions -- maybe not of the metabolic type,
22 but maybe in absorption, maybe there is some interaction
23 happening in the GI tract that is either facilitating
24 absorption or slowing it down. That's a possibility that
25 we really cannot give a firm answer to right now.

1 But I think what the message to say here is, is
2 that, in general, the pharmacokinetics from people with
3 leprosy versus normal volunteers are not that different.
4 There is this increase in peak, which we really can't
5 explain, but with the small number of subjects in this
6 trial, it is very hard to say that that is a very hard and
7 fast rule.

8 One was hoping -- and I understand now the
9 study has been completed -- we would get some more data
10 from the steady state study. Some of that information will
11 help us get a better idea as to what kinds of accumulation
12 kinetics we are going to see at steady state dosing. But,
13 again, I have not yet had a chance to review that
14 information.

15 Not to dwell too much on this graph -- there is
16 a lot of text up here -- basically, again, it goes over the
17 fact that there was a drug metabolism study done, that it
18 did look at the most common P450 isoenzymes, 1A2, 3A4, 2D6,
19 the ones that participate in a majority of all human drug
20 metabolism. They use a wide range of concentrations, pH
21 values, and really did a very good study, in terms of
22 looking at and trying to find metabolic interactions. I
23 think it was a very well-done study.

24 In effect, what you found was exactly what was
25 reported earlier, that thalidomide was not metabolized to

1 any significant extent by any of the common P450 isoforms,
2 and they used concentrations up to 40 times the peak plasma
3 concentrations seen with their highest dose. So, as I
4 said, it is a pretty good test, we think. And even
5 increasing the amount of enzyme, making it more than
6 normal, still did not cause any additional metabolism or
7 any change in the formation of metabolites.

8 From the other standpoint, you always like to
9 know, not only is the drug metabolized by the enzymes, but
10 what effect does it have on metabolizing enzymes
11 themselves. By repeating the study with control samples
12 with known substrates, it was found that thalidomide did
13 not participate in, did not inhibit, did not enhance any
14 drug metabolizing enzymes. So, in fact, it really
15 basically goes back to the conclusion that thalidomide is
16 not really a metabolic player in the P450 metabolism
17 scheme.

18 Again, some of these studies -- and I will go
19 through them very quickly for you -- have already been
20 discussed and have already been reported out.

21 The multiple-dose steady state study, which was
22 part of a clinical trial, some of those results have come
23 in. We have not yet had a chance to review them. Dr.
24 Colburn, again, went over them this morning.

25 The food effect study has already been discussed.

1 Special populations. Depending on what the
2 committee does, we can develop some kind of language for
3 that. Trying to do special population studies in a special
4 population already is especially very difficult. And with
5 the in vitro metabolism data, I think we can probably
6 address the hepatic without too much difficulty.

7 The renal is sort of a question mark, because
8 we really don't understand what is thalidomide broken down
9 into and where does it go. So, renal may still be an issue
10 we want to think about and give some thought to.

11 Drug interaction studies. Again, the oral
12 contraceptives study has been done and been reported out.
13 Again, we originally discussed at the previous advisory
14 committee some need for some other studies, possibly with
15 dapsons, possibly with rifampin, and other agents likely to
16 be given. I think now that we have the P450 information,
17 we may want to revisit that issue. If the committee has
18 any ideas or the sponsor themselves, that could be
19 revisited -- the need for those studies -- because we
20 clearly have this information, which really seems pretty
21 solid.

22 One thing I would like to apprise the committee
23 of is one of the original problems we had working with this
24 product was that thalidomide is just so insoluble as a
25 chemical substance. Its solubility in water is .06

1 milligrams per ml. If we were going to give a patient a
2 solution dose form of it, it would basically take about a
3 gallon of water to get the dose in, which really is not
4 very realistic for pharmacokinetic studies. Or even to get
5 the patients in and have them drink this in a short period
6 of time is not very realistic, especially for a drug that
7 undergoes hydrolysis.

8 Since then, we have been doing some research
9 with the FDA laboratories, and some solvents that are
10 feasible have been developed. The sponsor has committed
11 to, and we have had discussions about, a protocol. We have
12 sent comments back and forth. We are working with them on
13 developing a protocol where this will be looked at.

14 The advantage of this study is that by using a
15 solution dosage form, in addition to their oral capsule --
16 I won't go into the process, but through a process of
17 deconvolution of the plasma level time curve, we will be
18 able to look at the way that the thalidomide is absorbed --
19 a surrogate for bioavailability; it is not really
20 bioavailability -- but we will get a better assessment of
21 the rate and this issue of the flip-flop model, where we
22 have this continued absorption and continuing laid out, we
23 will be able to assess that degree from the study.

24 So, that's really going to be a very good study
25 and very useful from a pharmacokinetic standpoint. But

1 that is a planned study. We are still working with the
2 sponsor on that. And really, we are looking forward to
3 that one.

4 So, summing up, I guess the question is with
5 thalidomide: What do we know and what don't we know about
6 the pharmacokinetics? And really, I think, some of these
7 things should be considered as part of your deliberations
8 as to how you make and how you weight data, and what you
9 would like to see done in the future. If you have any
10 other ideas that you would like to suggest both to us and
11 the sponsor, or questions, we have some issues here that we
12 would like to have you consider and go over with you.

13 Starting off on the plus side of the ledger, we
14 certainly know that Celgene's product is bioequivalent to
15 what was used, both clinically studied and what they
16 propose for marketing. We know that we have dose
17 proportionality in exposure, but not in peak levels at
18 single dose. Whether or not that follows through to steady
19 state or that comes together is not known. We are, again,
20 hoping some of that steady state data, which they have
21 collected but we have not yet seen, may help us answer that
22 information. And also we are very interested in working
23 with them on the simulation work also, and trying to see
24 where it is going.

25 We think that it has similar pharmacokinetic

1 | characteristics in Hansen's disease patients. Yes, there
2 | were 2 patients who were aberrant, but in terms of their
3 | distribution and their elimination -- and when you look at
4 | those aspects of the curves -- they were very similar. It
5 | seems like what you were seeing is there may have been
6 | absorption change. And I think that may have been due to
7 | some other concomitant medications they were on.

8 | It is speculative, but it was a limited study,
9 | and I think that is about all you can really say. It's not
10 | a very solid study, because of its numbers.

11 | It is bio-inequivalent to the Tortuga form at
12 | single dose. Again, at steady state, at this point, we
13 | really can't say is it bioequivalent or not. I think the
14 | word this morning was very well chosen -- they said they
15 | were similar levels -- but what is similar? We tend to, in
16 | the agency, from a biopharmaceutics point of view, look at
17 | things from bioequivalency, using bioequivalency testing,
18 | which is a high standard, but it does allow, and has
19 | allowed, historically, for extrapolation from one
20 | formulation to another to another, applying a standard
21 | across all products.

22 | We don't believe it's very highly metabolized
23 | or participating in P450 mediated metabolism. It does
24 | undergo hydrolysis. In your package, in the review, I
25 | attached an article to my review which talked about, a

1 little bit, all the different potential hydrolysis products
2 and where they could go. And I think that is really the
3 unknown right now if you were to ask what happens to
4 thalidomide. Certainly, it gets broken down -- not by
5 metabolic means, but by hydrolysis. What happens to those
6 products we don't really know.

7 We looked, trying to use a technique we thought
8 was adequate, but it really didn't have the resolution we
9 needed. Whether or not this needs to be pursued, I think
10 we would like to get some feedback from the committee on
11 this and what techniques we should be thinking of.

12 Finally, what we don't know. Again, I will
13 modify this again from the presentation this morning. We
14 don't know the metabolic fate in humans. We don't. I've
15 already discussed that.

16 The relative bioavailability from the capsule
17 dosage form. We don't know that, but again, there are
18 steps being taken to address that and we have, I think, a
19 good plan underway to look into that issue. So, that is
20 going to be taken care of very quickly.

21 The importance of AUC or Cmax relative to
22 efficacy or safety is an unknown. There's not enough
23 information, we feel, from the pharmacokinetic database or
24 even from the published literature that makes us
25 comfortable one way or another. Again, we would be

1 interested in any input or insight people would like to
2 offer in that area.

3 Mechanism of action. Again, TNF-alpha has been
4 proposed, but the literature is very unclear there. Again,
5 that is not really a plus or a minus. There are many drugs
6 we don't know mechanisms of actions for, but we thought we
7 would put it up there anyway.

8 Effect of meals. Certainly that study has been
9 conducted and has been reported out. Once we receive it,
10 we will review it. From the preliminary information
11 presented this morning, it doesn't seem to really provide
12 any real changes in bioavailability or absorption. I think
13 there was some delay in time to peak, but that is not
14 really unexpected for most drugs.

15 Effect of gender. We do have the results --
16 well, we do not have -- the results are coming in from the
17 oral contraceptive study. And certainly that information
18 will help us deal with that issue of gender-related
19 pharmacokinetic changes.

20 Presence or absence of interaction with oral
21 contraceptives. Well, we have the study now -- well,
22 again, it's coming in -- with the Ortho Novums, and we will
23 be able to assess the pharmacokinetic interaction. I don't
24 mean to bring this up to start anything, but there is the
25 issue of the pharmacodynamic interaction. And there have

1 | been some discussions in the FDA about changing the way we
2 | do oral contraceptive studies. But what they did was the
3 | way we do them now.

4 | I think, in the future, you may see some
5 | changes in that. And we may actually ask the committee to
6 | give some feedback on that at a future meeting. But the
7 | tests they did right now were certainly consistent with the
8 | state-of-the-art that we are doing now. But I just wanted
9 | to let you all know that that may be changing, and we may
10 | be asking this committee to give some feedback, because of
11 | its experience with retinoids and other agents.

12 | We do want to talk just for a second about
13 | racemization. This is something I have always tried to
14 | bring up at every meeting, because it comes up again and
15 | again. There were some publications in the mid-1970s
16 | basically stating that the teratogenicity of thalidomide
17 | was due to one isomer, and that had we only given the other
18 | isomer, things would have been all right.

19 | I just want to beat that to death somewhat.
20 | New studies have shown that there is in fact rapid
21 | isomerization/racemization in vivo in humans, such that if
22 | you were to give the one isomer, you would produce the
23 | other in vivo, so that there is no way to get around it if
24 | it was assigned to one particular isomer. If you gave the
25 | R, you'd get the S in vivo, and vice versa. So, that is

1 not really an issue.

2 There is, however, a modest issue, and it is
3 from the literature and we are looking at it, regarding
4 about is there -- there appears to be -- or at least there
5 is a publication that suggests that there is a difference
6 in the rate of formation or the rate of interconversion
7 between the isomers, such that after a long period of time,
8 you might see an altered ratio. A true racemate is 50/50.

9 There's some suggestion that, with steady state
10 dosing over a long period of time, that the ratio might
11 change from 50/50 to 70/30, which is interesting
12 kinetically. From my standpoint, it's very interesting. I
13 think we will follow up on that, with getting some samples
14 in the steady state study, and looking to see if there is a
15 ratio change. But, beyond that, I do not think it will
16 enter into your discussions very much.

17 Pretty much, that's a synopsis of my review,
18 where we are at now and what our state-of-the-art thinking
19 is with thalidomide pharmacokinetics.

20 And, next speaker?

21 DR. McGUIRE: Dr. Bashaw, thanks very much.

22 Dr. Wilkin, are we going to hear from the
23 primary or the secondary reviewer in your division?

24 DR. WILKIN: No.

25 DR. McGUIRE: Dr. Michael Weintraub will give

1 an overview on which to base a regulatory action.

2 DR. WOODCOCK: Dr. McGuire?

3 DR. MCGUIRE: Yes.

4 DR. WOODCOCK: There certainly will be an
5 opportunity to ask the reviewers questions about their
6 reviews?

7 DR. MCGUIRE: Yes. I wondered if there was
8 going to be a formal presentation by either reviewer.
9 Thank you.

10 DR. WEINTRAUB: Good afternoon.

11 I am going to talk a little bit about the L.A.
12 data. Now, these data were gathered and analyzed by the
13 Food and Drug Administration, and the graphs I am going to
14 show you were presented to me by Dr. Gao and
15 Dr. Srinivasan, and also Dr. Steve Thomas.

16 Some aspects of these data are not the whole
17 syndrome of ENL. I did want to make that clear, because
18 Jon Wilkin had made the distinction -- what was the whole
19 syndrome and what was the cutaneous syndrome. So, we have
20 focused on the cutaneous syndrome in this particular case,
21 because we really don't have enough data on the whole
22 syndrome, and it's a little too difficult to discuss with
23 you.

24 Now, basically, what we are doing here is
25 looking at records kept for clinic purposes. These were

1 not necessarily records kept for research purposes. Yet,
2 they were very carefully kept, and I think can offer us
3 some very important insights. We're going to look at the
4 challenge and de-challenge and re-challenge of the
5 medication in the syndrome of cutaneous ENL.

6 Now, the first thing I did when I looked at
7 these charts, which was much different than the primary and
8 secondary reviewers, I separated them out and looked first
9 at a subset of patients who had only received thalidomide.
10 I felt that this was going to be one of the cleaner groups.
11 This may not be perfectly clean, but, in any case, they
12 only received thalidomide as their treatment for ENL.

13 When I did that, I separated out 46 of them.
14 The way they broke down were 24 of the 46, or about 52
15 percent, were positive; 15 were not wholly positive, but
16 were more negative -- or at least I called them negative;
17 and 7, we did not have enough data to really discuss the 7.

18 Now, looking at the first one, let me tell you
19 what we have here. It is never easy, I understand, to see
20 these slides. I wonder if you could move it up a little
21 bit, Mary Jane. Thank you.

22 On this axis, we have skin lesions: new
23 lesions, yes; new lesions, no data; new lesions, no -- not
24 no data, but no answer; thalidomide on; thalidomide off;
25 and the daily dose of thalidomide. Across the x axis, we

1 have the time in weeks, and this patient was on for nearly
2 900 weeks that we had some information.

3 But I show this first as an example of not
4 having enough information to make an understanding. Here,
5 although the patient was begun on thalidomide, we have no
6 data. The patient was begun on thalidomide, we have no
7 data. The patient was stopped on thalidomide, we have no
8 data. And we only have very sketchy data as to the amount
9 of the dose.

10 But, as I say, not to criticize these data,
11 these are common in a clinic-type setting. Now, you can
12 see I only have talked here about the cutaneous lesions.

13 Now, this next slide is over a 40-week period.
14 And the x axis changes on all of these. And, here again,
15 we have skin lesions, thalidomide on and off, and the dose.
16 We have a little more data here; no data actually for this
17 time point, so we don't know even where it was. We can
18 make an assumption, that the patient was begun on
19 thalidomide, but we have no way of knowing what was
20 happening. All we have is some very sketchy information
21 about the dose.

22 I wonder if we could have the lights down just
23 a little bit, because you can actually see the colors.
24 These are all colors. They are not as beautiful as
25 Dr. Bashaw's colors, but they are relatively --

1 This is an example of a single challenge and
2 de-challenge over a 50-week, or 1-year, period -- sort of,
3 about 42 weeks. New lesions was yes. The patient was
4 begun on thalidomide. Next time the patient was seen,
5 which was about 2 weeks later, no new lesions. And that
6 carried on.

7 Now, this particular time, there was no data
8 collected, but, soon after, when drug was still being
9 administered, no new lesions, no new lesions. Then,
10 although the thalidomide was stopped at this point, no new
11 lesions.

12 Now, what we can learn from these are some very
13 interesting points. First of all, the 100-milligram dose
14 was the initial dose. It dropped to 50 milligrams very
15 rapidly -- probably in the first month or so -- and then
16 continued 50 milligrams all this time, and then stopped.
17 So, we can see this is a very clean, very clear, single
18 demonstration.

19 The question comes up, however, what about
20 multiple administrations?

21 The patient had new lesions, was begun on
22 thalidomide and seen very quick. This is a 300-week axis,
23 but the patients were seen very quickly. The dose was 200.
24 This patient was kept on 200 for several weeks, with always
25 no new lesions, and then the dose was lowered to 100. No

1 new lesions again. The dose was kept was lowered to 50.
2 It went 200, 100, 50. And then the drug was stopped.

3 When next seen, the patient again had new
4 lesions, after being off the drug for some time, and
5 thalidomide was begun again. Unfortunately, because of the
6 way the data are collected, we have to do some inferring
7 here, but he was clearly off the drug before these new
8 lesions appeared. When seen actually a good many weeks
9 later, he was still on the drug. Lesions had disappeared,
10 no new lesions, and he was continued on that all along.

11 You can see here that the dose was 200
12 initially, 100, 50, back to 100 when the lesions recurred,
13 when there was recrudescence of his disease, kept on 100,
14 and that is where our data collection ended.

15 This, too, is a multiple episode of challenge,
16 de-challenge, re-challenge. This, again, is at week 0 of
17 the 170 weeks on the x axis. This time the patient was
18 seen when new lesions occurred. The drug thalidomide was
19 begun. We do not have any data on new lesions here, but
20 the drug was begun and kept on the same dose. Was seen
21 here with no new lesions. Again, no new lesions, no new
22 lesions. And the drug dropped from 200 milligrams
23 initially to 100 milligrams. Kept on 100 milligrams up to
24 here. Was taken off the drug.

25 Unfortunately, this was a so-called virtual

1 | visit. We had definite information that the patient was
2 | off the medication, but no data was obtained, because it's
3 | a virtual visit, just one to show that there was no drug
4 | being administered at that time.

5 | However, he returned, had new lesions. The
6 | drug was begun again. Then, out here, kept on the drug at
7 | 100 milligrams a day, and no new lesions.

8 | Now, here again, we have evidence that the
9 | patient was off the drug for some time. We definitely know
10 | he was off the drug. Then, when he returned, new lesions
11 | had occurred, and when the drug was begun again at a dose
12 | of 100 milligrams, the new lesions disappeared.

13 | These are the best examples one could say. A
14 | teacher of mine in medical school had discovered the
15 | Philadelphia chromosome, and one day in pathology class, he
16 | showed us a slide of the Philadelphia chromosome. He said,
17 | this is a typical example of the Philadelphia chromosome.
18 | Of course, I looked at 8,953 slides before I came upon this
19 | one slide which is typical. In any case, these are quite
20 | typical, believe me, of the various 24 positives.

21 | Now, these are examples of the failures. It's
22 | a little hard to see. In this case, there were new lesions
23 | and although the patient was seen quite rapidly -- this is
24 | a 600-week x axis. The patient was seen twice here, very
25 | rapidly, and did not improve on thalidomide. So, there are

1 two dots there.

2 When seen next, 2 years later approximately, it
3 was off drug, new lesions occurred, again was treated for
4 the new lesions. Again, there was no response. He was
5 taken off the drug, put back on the drug, and then there
6 was a recrudescence lesion. And, as I said, this is a time
7 when we are sure he was off the drug. It was begun again,
8 and this time had some success.

9 However, we can't really interpret this success
10 as cleanly as we could the other, because, despite the fact
11 that he was on thalidomide, in both cases, there was a very
12 delayed response, if any response, because we don't have
13 any data showing a response, and I called this a failure.

14 The one thing we can get from the dosing
15 information, 100 milligrams did not seem to help him. He
16 was given 200 milligrams the following time and tapered to
17 100 milligrams, but again, may have been helped, or it may
18 have just been the passage of time.

19 So, you can see that some of the recrudescences
20 can occur on thalidomide itself. And here is one where the
21 patient was off of thalidomide, no new lesions. Was put
22 back on thalidomide. And it is, again, a little hard to
23 tell about the timing, but it is possible that this first
24 episode was treated with thalidomide, but it is unlikely.
25 And here, was off the medication and on the medication, and

1 may have, again, had a response.

2 However, we have no information here about this
3 patient being off the medication. And it may have been
4 that he had continued on the medication at 100 milligrams a
5 day and had a recrudescence of the disease while on
6 thalidomide. It's possible.

7 Again, here, this appears to be a recrudescence
8 on thalidomide. Here he was off thalidomide. We do not
9 have good data, but there is a possibility of more disease.

10 Now, this next patient -- this is the first 300
11 weeks of his course -- was on therapy for a very long time.
12 You can see, again, that there may have been a
13 recrudescence while on thalidomide. However, this dot
14 indicates that he was off thalidomide again, put back on,
15 and had a decrease in his skin lesions.

16 So, you can see, this is a mixed case, but I
17 decided that, in looking at it and investigating it, that
18 in fact this was a negative case. You can make an
19 argument, but it's what I took as a negative case.

20 Now, the issue of steroid sparing. There were
21 56 patients on a combination of steroids or clofazimine,
22 and I decided not to look at the clofazimine patients.
23 There were not very many of pure clofazimine alone. There
24 were a number on prednisone.

25 Here are the new lesions, no data; no new

1 lesions; prednisone on, prednisone off, prednisone daily
2 dose; thalidomide on, thalidomide off, and the daily dose
3 of thalidomide. Here is a good response to thalidomide,
4 with prednisone and thalidomide together. However, you can
5 see that the thalidomide was gradually tapered over a year
6 period, and was stopped at this point here.

7 The thalidomide, however, was carried on for
8 another probably close to a year, 40-some weeks, and was
9 stopped at this point. And, again, he recrudesced, had a
10 lot of lesions when the thalidomide had been off. And then
11 thalidomide was started again and his lesions returned to
12 no new lesions.

13 Also, however, the thalidomide was continued
14 here, once it had been restarted, and then it was dropped
15 to 50 milligrams, and then to nothing. But with the second
16 episode, there was no prednisone given. So, there were two
17 pieces of evidence here that it was steroid sparing.

18 Then, for one last look, a little more
19 complicated patient. This was a patient who had new
20 lesions but was treated only with thalidomide for the first
21 episode. Thalidomide was stopped. He was off thalidomide
22 and off prednisone for the second episode. And then had
23 what we can only infer was a pretty serious episode of new
24 lesions. He was begun on prednisone, begun on
25 thalidomide at a high dose of 200 milligrams a day, and the

1 prednisone was tapered. The thalidomide was continued for
2 almost a year, and then the thalidomide was gradually
3 tapered, till it was finished.

4 Although we do not have any data here -- all
5 these points indicate no data -- our evidence is
6 thalidomide was continued, as I say, for approximately
7 another year, and steroid sparing was seen, because the
8 steroids were stopped at this level and then carried, and
9 the thalidomide wasn't stopped till 190 weeks.

10 So, that shows you the kinds of data that we
11 got from the L.A. study.

12 If we looked only at the skin manifestations,
13 not the systemic manifestations, I think we can say some
14 things about the skin manifestations.

15 We can also learn a little bit about the dose.
16 It appears that 100 milligrams is a good starting dose, as
17 was mentioned by the company, but we really did not have
18 much information on that. Probably 100 milligrams for 2
19 weeks, and if no response is achieved, raise the dose to
20 200 milligrams or to 150 milligrams, and then higher if
21 necessary.

22 These data were derived from case report forms
23 that were analyzed at the FDA by some people in this room,
24 and we are very grateful for their work, because they did a
25 very good job.

1 Now, we can't get much safety data out of this
2 area. And you say, well, how can you say 52 percent,
3 whereas this morning we heard 90-some percent?

4 Well, let me tell you, that is what I tried to
5 stress this morning. People of good faith can look at the
6 same dots on the same graphs and either see a response or
7 non-response, and, more importantly, I think that what we
8 see here is pretty good evidence of efficacy of the
9 medication, that there were responses to the medication.
10 52 percent may not be great. It's a lot better than other
11 things that we had -- at least in the thalidomide-alone
12 group.

13 Some people might say, well, if you looked at
14 these, and you might find that the data will change. If
15 you look very closely at these, you find that they were on
16 perhaps ibuprofen or aspirin or something else. They may
17 have been on ibuprofen or aspirin, and that is why we
18 stuck, again, to the skin lesions of ENL.

19 I think I'll stop at this point and see if
20 there are any questions, Dr. McGuire. And I remember that
21 this is your laser pointer.

22 DR. MCGUIRE: That was important.

23 My preference would be to go ahead through the
24 rest of the FDA presentations.

25 DR. WEINTRAUB: Good.

1 DR. MCGUIRE: And to get my laser back.

2 (Laughter.)

3 DR. MCGUIRE: I'm sorry, I didn't introduce the
4 next speaker. He is Dr. Murray Lumpkin, and he will talk
5 about the various distribution options.

6 DR. LUMPKIN: Good afternoon, ladies and
7 gentlemen. I appreciate the opportunity also of being here
8 with you this afternoon.

9 I do not want you to think, by our putting a
10 point here of talking about different distribution options,
11 that this in any way signifies a predetermined outcome, in
12 the sense that we are talking about post-approval
13 distribution here.

14 But as you heard this morning, one of the real
15 issues surrounding the whole risk/benefit analysis for this
16 particular product deals with one of the issues about how
17 does one try to manage risk in the 1990s.

18 There have been a lot of parallels drawn today
19 between life as it was in the 1960s when this product first
20 came around and life as it exists now. Now, for many of
21 you in this room, who are as old as I am, you remember the
22 1960s as the time that you went to grade school. But what
23 I understand from the scientific approaches and the
24 regulatory approaches that existed back in the 1960s, the
25 big challenges that those individuals faced was, how do we

1 establish efficacy? How do we determine risk?

2 And these were challenges just simply trying to
3 identify whether products really worked and what the risks
4 were and how to identify those risks. And you see what
5 happens when you don't have good, clean data to try to
6 establish efficacy, and we've seen what happened with this
7 product when you do not have good ways of trying to
8 identify risk.

9 Now, that was a challenge that the people back
10 in the 1960s were faced with. And I think when we look at
11 the sophistication in drug development programs that have
12 occurred in the last 35 to 40 years, we have become much
13 better in learning how to identify risk.

14 But what our challenge is now is how do you
15 communicate that risk and how do you manage that risk
16 because it is not only an issue of identifying it and
17 putting it into the equation because you know it happens,
18 it is now an issue of saying, before you determine that
19 equation of benefit and risk, if we know there are risks,
20 are there ways that we can manage it so that the benefit is
21 even perhaps better than what we thought it was, or at
22 least in that equation.

23 So, that brings us to the role, then, of
24 restricted distribution and monitoring systems. This is
25 something that is really very hard for us in this country

1 | to deal with. It is kind of one of these quintessential
2 | American dilemmas of societal goals versus individual
3 | rights, and how do you balance those in a free society.

4 | All of us are fairly familiar with how drugs
5 | generally get distributed in this country, and it is a
6 | distribution system that has served us well. If you think
7 | that once a drug is approved in the United States, very
8 | quickly thereafter you as a patient, your health care
9 | practitioner and your local pharmacist, no matter whether
10 | you are in Maine, Hawaii, above the Arctic Circle in
11 | Alaska, or Key West, throughout this entire continental
12 | span of land mass, that product is generally there and
13 | generally available without a lot of hassle for the
14 | patient, for the prescriber, and for the local pharmacist.
15 | And that is the way our system has served us well over the
16 | last century that we have basically had it.

17 | So, now when we start talking about restriction
18 | distribution or modifying distribution to manage risk, it
19 | begins to raise a lot of whistles and bells and questions
20 | that people have to deal with.

21 | As you've heard already today, this is
22 | something that, although it is not something we have a
23 | great deal of experience with in this country, it's
24 | something that we do have some experience with. And there
25 | are things that I think we have learned from the

1 | experiences that we have had to date.

2 | I am not going to talk a great deal about
3 | Accutane. You have heard about Accutane a great deal
4 | already today. This committee is very familiar with this
5 | particular program of trying to manage risk by a very
6 | large, heavy educationally oriented type of program. But
7 | it's a program that did have loopholes. And it's a program
8 | that is essentially around 10 years old now, and it's a
9 | program that I think we, as a community, have learned a
10 | great deal from.

11 | As you heard this morning from the people from
12 | Celgene, I think they have tried very hard to look at this
13 | program and say, what were the good parts of this program,
14 | what can we learn from this program, and where were the
15 | loopholes, where did it tend to not accomplish its goal,
16 | and how can we try to make sure that does not happen if we
17 | do get an approval and go to a restricted distribution
18 | system in this country?

19 | You've also heard about Clozaril and the
20 | program that that particular product had to try to manage
21 | the known risk of agranulocytosis with this particular
22 | product. I think one of the very important lessons that we
23 | learned from this particular program is that if you make it
24 | too tight up front, you might have great, 100 percent
25 | compliance, but you do get to the point where those

1 individuals who actually have to implement the program --
2 the physicians, the other health care prescribers, the
3 patients -- they say no, it's too burdensome; it's not what
4 we can stand on a day-to-day basis.

5 So, with Clozaril I think one of the things we
6 learned, from the original program in 1990 to the program
7 that we now have that came into being in 1992, is that you
8 need to have a program that meets the needs of this very
9 large country that we've talked about, that allows local
10 areas to implement a quality assurance program to assure
11 that the kinds of distribution controls that you have
12 implemented indeed can be implemented by the pharmacists,
13 by the health care practitioners, and by the patients who,
14 in the end, are the ones whom we are all trying to serve.

15 Now, there is one other example that we have
16 had that has not been mentioned. And it is a little bit
17 different of a product, and that is the product called
18 fentanyl Oralet. For those of you that know something
19 about this particular product, fentanyl is a pain
20 medication, a very potent pain medication, that has been
21 available in this country for a great period of time.

22 There were problems with a patch version of
23 this particular product, where the patch was being used in
24 ways that put people at risk. And we did have some very
25 bad outcomes because of particular off-label and

1 | inappropriate use of the fentanyl patch. So, when it came
2 | time to look at a different formulation, which basically,
3 | for lack of a better word, was more of a Popsicle kind of
4 | presentation of this particular product for children, it
5 | was a tremendous advance in trying to come up with a
6 | formulation that allowed children to benefit from the
7 | benefits of this particular drug product, but it also made
8 | it, as a presentation to children that was obviously a
9 | presentation of a very, very potent, potentially dangerous
10 | drug product.

11 | It was a product that primarily approved for
12 | use in hospitals as a preoperative product for use in very,
13 | very painful procedures and these kinds of things.

14 | There was a program that was put into effect
15 | that basically limited its distribution to hospitals and
16 | institutions who had gone through a fairly rigorous
17 | educational program and who indeed showed that they had the
18 | resuscitative equipment available, that they had the staff
19 | available, and that, indeed, they could use this particular
20 | product in children in a way that they would manage the
21 | risk and perhaps very, very muchly decrease the potential
22 | risk of this particular product when it's used in children.

23 | One of the points, though, I do want to make is
24 | that all of these three were basically done as a voluntary,
25 | cooperative kind of endeavor by the pharmaceutical

1 manufacturers who sponsor these particular products, very
2 similarly to what you heard this morning. These were very
3 responsible companies who have tried to look at this and
4 say, what can we do, what can we realistically do to assure
5 as much access to this product as possible for those who
6 need, but, on the other side, to try to manage the risk in
7 the best way possible in the 1990s?

8 Well, as we've looked at this, I do want to
9 tell people that we do have a provision, and it's a
10 provision in our regulations that we have not used yet. It
11 is a fairly new provision. It came in as part of what are
12 called the subpart H regulations. These are the
13 regulations that deal, in one part of them, primarily with
14 the accelerated approval of drugs under the surrogate
15 endpoint provisions that we have used on several drugs thus
16 far.

17 As you know, this particular group of
18 regulations refer to drugs that treat serious diseases or
19 that treat life-threatening illnesses, and they refer to
20 drugs that provide meaningful therapeutic benefit to
21 patients over existing treatments. Once you look at this
22 group of drugs, then this particular series of regulations
23 have two different components. One I have mentioned, the
24 idea of saying that we are allowed to approve drugs that
25 meet these definitions on a surrogate endpoint under the

1 | accelerated approval.

2 | Then the second part, not dealing with
3 | surrogate endpoints at all, basically says that if the
4 | agency concludes that a drug product is shown to be
5 | effective, but could only be safely used if distribution or
6 | use were restricted, FDA will require such post-marketing
7 | restrictions as are needed to assure the safe use of the
8 | drug product.

9 | And then the regulations go forward and give
10 | just a couple of examples. It does not limit it to these
11 | kinds of restrictions, but it gives these as examples. And
12 | they are very similar to the kind that had been worked out
13 | previously with the products that I talked about, or the
14 | kind that one sees that the company this morning talked
15 | about in their proposed distribution plan.

16 | For example, restricting distribution to
17 | certain facilities or to certain physicians or other
18 | practitioners who have special training or experience, or
19 | distributing the product on the condition that there be
20 | performance of specified medical procedures.

21 | So, this idea of having a restricted
22 | distribution system, although one we have not used
23 | frequently in this country, it is one that is in our
24 | regulations, it is one that we can use. I think it is one
25 | that, when we have not used it in a mandatory sense, but

1 | when we have used it in a cooperative sense, in a voluntary
2 | sense with the sponsors, we have had a period of learning
3 | over the decade of the 1990s.

4 | What you saw today, I think, is the beginning
5 | of the discussion of taking the bits and pieces that we
6 | have learned from Accutane, that we have learned from
7 | Clozaril, that we have learned fentanyl Oralet, and said,
8 | now that we look at this product, how can we manage, how
9 | can we communicate the risks that we know about thalidomide
10 | to the patients, to the practitioners, to really try to
11 | manage this risk such that the benefit will be available to
12 | those who need it?

13 | That's our spiel on the ways that we can look
14 | at restricted distribution at this point in time. I give
15 | it you in the audience, I give it to you on the committee,
16 | as just a foundation to begin the discussion of the
17 | proposal that was put on the table this morning by Celgene
18 | as we get to the questions tomorrow. And if we get past
19 | the basic efficacy and safety and the recommendation is
20 | that people feel that the benefits outweigh the risks, then
21 | we can further get into a discussion of how to manage those
22 | risks under these kinds of provisions.

23 | I thank you for your attention, and now Lou
24 | Morris is going to talk to you a little bit about looking
25 | at the Celgene proposal -- just some other ideas that we

1 had had as we had begun to look at this, that might enhance
2 their proposal a little bit further.

3 DR. McGUIRE: For those of you who do not know
4 Dr. Morris, he is the supervisory psychologist in the
5 Division of Drug Marketing, Advertising and Communications.

6 DR. MORRIS: Thank you. Good afternoon. It is
7 a pleasure to be here.

8 We heard this morning from Mr. Williams about
9 Celgene's STEPS program. It is a system for thalidomide
10 education and prescribing safety. I think the fact that
11 it's a system is very important. It shows that it is
12 thoroughly thought through. There are three elements to it
13 that I discern.

14 One is the communications elements. And that
15 is composed of a series of brochures and a consent sheet
16 that's very thorough. I think if one reads through these
17 materials, one clearly gets the concept that this is a very
18 thorough message. It's very consistent. It's very
19 concrete. I think it clearly demonstrates that the message
20 is there.

21 If one looks at the distributional elements of
22 it, I think it's very innovative in that it uses not only
23 pharmacies that agree to keep a system in place, but it
24 actually uses a consent sheet and the pregnancy test as
25 tickets that people need to get their medicine. It

1 | certainly goes beyond existing programs.

2 | A third part of the program that I think is
3 | very important is that it sets up at least the potential
4 | for a quality control check. I think the mandatory
5 | registry is very important in that regard. I think that we
6 | should be humble enough to realize that we cannot, up
7 | front, design a perfect system, and testing it and making
8 | sure it's right is something that is very important.

9 | However, we've heard and we will continue to
10 | hear some concerns, and here are some that we have
11 | discerned.

12 | The first thing is consumer understanding.
13 | These are some very, very difficult concepts for people.
14 | And we do know that the literacy of the population is
15 | something that suggests that at least 20 percent of the
16 | population have an awful lot of difficulty reading
17 | anything, and another 20 percent are sometimes considered
18 | functionally illiterate, because, even if they do read,
19 | they have difficulty with complex concepts.

20 | The solution is not making something at a
21 | third-grade level. It is explaining it well enough so that
22 | people have a true understanding of the information.

23 | A second concern is that the people who will be
24 | obtaining thalidomide -- it is a whole new world out there.
25 | When I say the word "thalidomide," I think people in the

1 audience here conjure up very vivid memories, as Mary
2 Pendergast mentioned. The median age in the U.S.
3 population is 35. Most people weren't born when the
4 thalidomide tragedy occurred. I have a little bit of data
5 I will be sharing with you in just a second on that.

6 The third concern is, although the system is
7 thought through and is well designed, real questions on how
8 health professionals will follow through with this, it is
9 just unclear. I think we are asking an awful lot of health
10 professionals.

11 How will the system actually operate? I think
12 we have to pay attention to that.

13 Here is some data. We have started a study on
14 over-the-counter drug labels. The study is being conducted
15 in eight shopping malls around the country. And as of 5
16 o'clock last night, we have been -- this is literally hot
17 data. We asked a very simple question in that survey, and
18 that was, we asked people, could you define what the word
19 "thalidomide" was as if you had seen it in a dictionary?
20 And what percent would even venture a guess?

21 Overall, about half the people said they don't
22 know. This is just the females. We wanted to see if there
23 was a gender difference. There were 77 females. Just as
24 you would expect, age breakdowns. The people who were in
25 the younger age groups didn't know or were wrong. People

1 | who were over 40 were more likely to get it correct or
2 | partially correct. So, half the people do not know what
3 | thalidomide is. It's just what you would expect.

4 | The next one for males is a very similar set of
5 | data. We didn't see any obvious visual differences in
6 | looking at the data. But, again, young males don't know.
7 | Older ones are more likely to get it right.

8 | These data are highly preliminary. We will be
9 | continuing to collect it. It is only 130 subjects, so it
10 | is not conclusory. But I think it does suggest what we
11 | expect, which is that there is clearly the age difference.
12 | And you just cannot assume that when you say the word
13 | "thalidomide," there is a vivid memory, and I think a vivid
14 | memory is very important in terms of how people are going
15 | to use this product.

16 | Yes?

17 | DR. DUVIC: That is really interesting data.
18 | And given that data, shouldn't we just have the word
19 | "thalidomide," and not have two different names for this
20 | drug? Because Synovir sounds like an antiviral for herpes
21 | or something. For the purpose of educating the public,
22 | which is going to need to be done for this, shouldn't it
23 | just have one name, and that name be thalidomide, for
24 | historical reasons?

25 | DR. MORRIS: But half the people do not know

1 | what thalidomide is.

2 | DR. DUVIC: I understand that. And so even
3 | less are going to know Synovir, once you start having a new
4 | name for it.

5 | DR. MORRIS: Well, I think it is important to
6 | have a clear communication objective. How we do that is
7 | something I think we can -- you know, we are willing to
8 | listen to those suggestions at this point. But I do not
9 | know. You mean not have a trade name on it? Is that what
10 | you are suggesting?

11 | DR. DUVIC: That's right.

12 | DR. MORRIS: Well, I think that's something the
13 | committee should certainly debate.

14 | DR. McGUIRE: That's something that was
15 | discussed at the November meeting.

16 | DR. MORRIS: Okay. Well, let me just raise
17 | some ideas and some suggestions.

18 | In terms of how people use this product, one of
19 | the things that I am concerned about in terms of what
20 | Celgene is suggesting is that they are suggesting two means
21 | of education. One is health professional counseling and
22 | the other is a series of written information. I think that
23 | having something in between -- audiovisuals, a tape or
24 | something like that -- I think could be a tremendous
25 | improvement here for a couple of reasons.

1 One is I think it is just very important to
2 have a very vivid message. I do not know if written
3 communication does that. Having and audiotape that people
4 can think about and envision and explain things, I think
5 can be very important. I think it could be integrated to
6 the informed consent process, and I think it is something
7 that we should think about.

8 The next suggestion, and I think it is
9 something that we have heard this morning, is that health
10 professional incentives and training is very important.
11 One of the things I liked about Celgene's proposal is that
12 they use the word "system." And I think if we think of
13 this as an error prevention analysis system that we do in
14 medication errors -- a way of not thinking about
15 individuals, but thinking about a systems approach to
16 prevent errors -- is a nice way to think about it. And I
17 think that having health professionals integrated into a
18 system would be a way to decrease the likelihood of some
19 error occurring.

20 The third concern, and I guess a suggestion for
21 some vigilance, is simply to think about quality control
22 not only in terms of the initial system, but what is going
23 to happen over the long term. One of the things we know
24 about behavioral compliance is that written information can
25 improve short-term compliance, but long-term compliance is

1 | very hard.

2 | So, I think, as part of the quality control, to
3 | worry not only about the people who initially get it and
4 | what they understand but, over the long term, what do they
5 | actually do.

6 | Those are some of the things I would like to
7 | suggest.

8 | I thank you, and I would be happy to answer
9 | questions.

10 | DR. MCGUIRE: I know there are many questions
11 | from the committee. I would like to have a micro-break and
12 | reconvene at 3:30. Please have the presenters from the FDA
13 | back at 3:30, and we will have the committee, so we can get
14 | directly into the questions. There are lots of things to
15 | be answered.

16 | (Recess.)

17 | DR. MCGUIRE: Ladies and gentlemen, I would
18 | like to reconvene the afternoon meeting. Please, can the
19 | committee be seated and the representatives of the agency.

20 | First, I would invite questions from the
21 | advisory committee to the representatives of the agency:
22 | Drs. Wilkin, Hill, Bashaw, Weintraub, Lumpkin, and Morris.

23 | Dr. Bergfeld.

24 | DR. BERGFELD: Yes, I have a question of
25 | Dr. Dennis Bashaw, and that has to do with the metabolites.

1 I understand from all the presentations this afternoon and
2 even this morning that the metabolites of thalidomide are
3 not totally known, nor is the mechanism of metabolism or
4 excretion totally understood. And I wanted to know what
5 would be recommended to understanding this better.

6 DR. BASHAW: The way it is normally done, and
7 the way it has been done in the past in this area, we try
8 to use in vitro data and in vivo data to come up with
9 different approaches. And we thought that the study we had
10 in the Hansen's patients, looking at the parent and the
11 three, what we considered, most likely metabolites -- and
12 this was done in consultation with the sponsor and their
13 consultants -- would be an appropriate way. However, as
14 you know, it didn't work out.

15 The next step to go to, or one to consider,
16 would be, of course, to use a radio-labeled trial, most
17 likely with a carbon-14 label, because if it does undergo
18 hydrolysis, putting a tritium label on there would be the
19 last thing you would want to do, because it would just go
20 everywhere as part of the hydrolysis process. But that
21 would probably be the next step if the committee felt that
22 we should pursue it further -- would be a carbon-14 study.

23 DR. BERGFELD: Well, I need to ask a follow-up
24 question. I don't understand that we would consider a drug
25 that we did not understand its metabolism in some way, when

1 it has such a terrible outcome if given to specific women.

2 DR. BASHAW: Well, I think we do know some
3 about the metabolism. I don't think it is totally a black
4 box, although one can quibble about some of the P450
5 information, but those in vitro studies clearly indicate
6 that the major routes of drug metabolism, it does not
7 participate in, and that the product should be ones of
8 hydrolysis.

9 As I mentioned in my presentation, in my
10 review, there is an article I extracted. I think it
11 proposes something on the order of 18 potential hydrolysis
12 metabolites. And that certainly multiplies the difficulty.
13 You get small amounts, a few percent here, a few percent
14 there.

15 Normally, yes, we certainly do know more about
16 metabolites. But, oftentimes, when we do approve drugs, we
17 have just general ideas about metabolism -- maybe 30 or 40
18 percent identified, not 100 percent identification of
19 metabolites. That is really very rarely accomplished that
20 we know exactly what it's always broken down to.

21 I think that where hydrolysis is a major
22 mechanism, and again, if you look at the structure of
23 thalidomide, it has got all those carbonyls hanging off of
24 it, that it has got so many places for hydrolysis to grab
25 onto, it just really complicates the matter. And that is

1 | what defeated our earlier efforts. We made an attempt, but
2 | it just didn't work.

3 | DR. BERGFELD: Well, can I ask you another
4 | question?

5 | Would that same be the answer for not knowing
6 | enough about how it is eliminated?

7 | DR. MORRIS: I'm sorry? Could you repeat that,
8 | please?

9 | DR. BERGFELD: Your description of why the
10 | complication of understanding its metabolism and the need
11 | for another study or studies to understand that, is that
12 | the same answer that would be given for understanding the
13 | elimination?

14 | DR. BASHAW: Yes, ma'am.

15 | DR. McGUIRE: Dr. Orkin?

16 | DR. ORKIN: I would like to ask a question of
17 | Louis Morris. I asked him this just a moment ago, but I
18 | thought I'd put him on the carpet. And that is, is it
19 | possible to design a very simple exam that a person would
20 | have to fill out before they get the prescription? And
21 | maybe that should have done with Accutane.

22 | DR. MORRIS: Yes, sure, anything is possible.
23 | In fact, I would suggest, if you look at the informed
24 | consent sheet, one of the items says, I understand the
25 | material. And how do people know that, if they understand

1 | it or not?

2 | I think building that into the health
3 | professional counseling would be a good way of doing, so a
4 | health professional can assess the extent to which people
5 | do know about the product and understand its risks and ask
6 | question in an open-ended way, to check people's
7 | understanding. I think that is something that could be
8 | designed into the program.

9 | DR. ORKIN: And maybe that could be a follow-up
10 | to your suggestion about the audiovisuals, to see that they
11 | do comprehend this.

12 | DR. MORRIS: Yes, I think if it is done in a
13 | way that involves the patient, the more the better.

14 | DR. MCGUIRE: Dr. Shannon?

15 | DR. SHANNON: Yes, I would like to make a
16 | comment.

17 | There is a heck of a lot known about the
18 | metabolism of this drug, quite frankly. This has been
19 | presented. And it is very labile at the amide binds, and
20 | we know right where it hydrolyzes first and what are the
21 | products. So, in the literature, in the early heydays of
22 | thalidomide, it was looked at thoroughly, so there's a lot
23 | known.

24 | What I would like to share -- and it was very
25 | nice to see these elegant slides, with all the

1 | pharmacokinetics and so forth and doses, and it was also
2 | good to see this confirm what we know previously, and that
3 | is that you achieve about a maximum blood level of about 1
4 | to 2 micrograms, despite the regimens that you take.

5 | The other thing is that Dr. Kilpatrick had
6 | mentioned about a low zone tolerance, as far as -- and I am
7 | maybe reading too much into his question -- but it has been
8 | known that ingestion of one 100-milligram tablet of
9 | thalidomide during the first trimester of pregnancy caused
10 | a fetal malformation.

11 | The other thing that is the other good side of
12 | thalidomide that Dr. Hill had alluded to was possibly
13 | aspects of poor solubility with the aspect of 60 micrograms
14 | being the maximum solubility constant of thalidomide in
15 | water. What I would like to also suggest is one of the
16 | reasons you cannot, presumably -- and I do not know this
17 | factually -- but one of the speculations is the reason you
18 | cannot overdose with thalidomide is very simply that it
19 | forms dimers. It forms dimers in the gut, and these are
20 | most likely eliminated quickly. And if it is absorbed in
21 | the GI tract, those are probably eliminated more quickly.
22 | There have been cases where people have tried to take grams
23 | to overdose with thalidomide and have not had any problems.

24 | The point also that has made a lot, again, with
25 | doses. It looks like the maximum blood level achieved,

1 | despite the regimen, is 2 to 3 micrograms per ml, where
2 | maybe in GBH reaction, where they have got some problems
3 | with gut motility, you might achieve 20 to 25 micrograms
4 | maximum. Whether or not that's relevant for clinical
5 | efficacy and so forth, but that is generally considered to
6 | be the plasma hydrolysis concentrations of thalidomide.

7 | But, again, in point of fact, there's an awful
8 | lot that is known about the metabolism and so forth and the
9 | breakdown.

10 | DR. MCGUIRE: Mr. Warren?

11 | MR. WARREN: I guess I would like to address my
12 | comments to Mr. Morris and that is regarding the education
13 | plan and everything that I had seen about the lack of
14 | education on behalf of American women. From a preliminary
15 | point of view, 48 percent of them didn't know what
16 | thalidomide was. That frightens us, obviously, from the
17 | Thalidomide Victims Association of Canada.

18 | So, should this ever be licensed, I would just
19 | suggest -- I liked what I saw about audiovisual
20 | communication and that kind of thing -- and I would suggest
21 | that that maybe is a role, where the victims of thalidomide
22 | should certainly make the impact statements that would be
23 | useful.

24 | My question comes down to the various
25 | distribution options and how that is actually implemented.

1 I liked better what I saw under mandatory regulations. I
2 think it would have more teeth. So, my question comes down
3 to, is it really a difficult thing to go towards a
4 mandatory distribution process over a voluntary
5 distribution process?

6 DR. McGUIRE: You are looking at me, but you're
7 talking to Dr. Lumpkin I think.

8 MR. WARREN: Yes; I'm sorry. I am looking at
9 you because that is who I was addressing.

10 DR. WOODCOCK: I'm Janet Woodcock.

11 The need to impose a mandatory restriction,
12 under regulation, depends on our judgment of whether that
13 is necessary to ensure the safety of the product. So, it
14 really depends on how safe we feel the safety would be
15 under a voluntary system or whatever safety is available
16 compared to the need for additional safety that would
17 merit, that would require for approval a restricted
18 distribution.

19 DR. BERGFELD: Could I ask what drugs are under
20 the mandatory distribution?

21 DR. WOODCOCK: There has not been any, as
22 Dr. Lumpkin said. There have been no drugs approved with
23 that part of those regulations to date.

24 DR. McGUIRE: Dr. Kilpatrick, you have been
25 very patient.

1 DR. KILPATRICK: Thank you, sir.

2 I'd like to ask two questions, following up on
3 both the remarks that have been made recently. One, again,
4 to Dr. Lumpkin, about restricted distribution. Does the
5 agency have the authority to withdraw approval if
6 restricted distribution is not working?

7 DR. WOODCOCK: Under the accelerated approval
8 regulations, there are provisions for more rapid withdrawal
9 of approval. Under our ordinary regulations, under
10 ordinary approvals, it is somewhat difficult for FDA to
11 rapidly withdraw a drug from the market. It is usually
12 voluntary by the manufacturers. But we can do it.

13 DR. KILPATRICK: But we are talking over a long
14 period about a system which may degrade or deteriorate over
15 time, and we're talking about a monitoring system which may
16 be very effective initially. But my concern is that, if we
17 go this direction, the agency may in fact be in the job of
18 monitoring a monitoring system, which is getting rather
19 laborious.

20 Coming back to the other question about dosing,
21 do I take it, sir, that there is no such thing as an
22 optimal regimen for the treatment of ENL with thalidomide,
23 from what you were saying?

24 DR. SHANNON: I am not in clinical medicine,
25 and I wouldn't speculate on that. I just know that for

1 | severe ENL, generally 100 milligrams, four times daily, is
2 | what's started off. And I would have to refer that to Dr.
3 | Rea and Dr. Yoder. But each physician has his own
4 | particular regimen. But that is probably the highest dose.

5 | The problem is you are hearing thalidomide
6 | being recommended be used at gram quantities in one
7 | ingestion time. My thoughts on that would be it is
8 | probably a waste of the drug, in the sense that it is going
9 | to just be excreted or through the gut, and so forth.

10 | DR. KILPATRICK: Dr. McGuire, is this something
11 | that the sponsor will be undertaking? I know it may not be
12 | required by FDA, but have they plans to go forward beyond
13 | the current Philippines study of 100 versus 300 milligrams
14 | into what might be a more effective dose regimen?

15 | DR. MCGUIRE: Of course, I do not know the
16 | answer to that. The Philippines is in process. It is not
17 | complete by any means.

18 | DR. KILPATRICK: I am asking actually do their
19 | plans go beyond that? That will certainly not answer all
20 | of the questions that it might raise.

21 | DR. MCGUIRE: I think if the agency asked them
22 | to go beyond that, they will.

23 | DR. KILPATRICK: Thanks.

24 | DR. MCGUIRE: Dr. Woodcock.

25 | DR. WOODCOCK: Thank you.

1 I just wanted to clarify something you were
2 discussing about ongoing safety and monitoring a monitoring
3 program. Just as we have with many other drugs, the
4 experience in the marketplace may reveal that the safety of
5 the product that was believed to be present in the
6 pre-approval evaluation, the product is less safe when it
7 gets on the market, there are unexpected adverse reactions,
8 or sometimes there are other kind of problems, such as
9 failure of the safeguards that were put into place.

10 So, this is not an unusual or unexpected
11 situation if it were to occur, and we have to take
12 measures. I believe some products have been brought back
13 to this advisory committee sometimes because of safety
14 problems that have occurred post-marketing. So, that would
15 be something that we would expect to happen.

16 DR. KILPATRICK: Thank you.

17 DR. McGUIRE: Mrs. Cohen.

18 MS. COHEN: Dr. Lumpkin said he went to grade
19 school in the 1960s. I would hate to tell you when I went
20 to grade school.

21 (Laughter.)

22 MS. COHEN: But I have some historical memory
23 of DES and Norlutin and the problems that it caused.

24 I also, in another life, which I do not even
25 think the members know, was a licensing coordinator and

1 | program certifier for group homes for the developmentally
2 | disabled and the mentally disabled. And I can tell you,
3 | I've seen the traumas that it causes in families and the
4 | disruption and the divorce and everything else that goes
5 | with it. So, I have this in my mind, and I would like to
6 | have it dispelled. And I hope we will be able to do it.

7 | I have a couple of questions. One, I am going
8 | to put my foot in my mouth, but the other one I did
9 | already.

10 | DR. KILPATRICK: The other foot?

11 | MS. COHEN: The other foot.

12 | (Laughter.)

13 | MS. COHEN: It was bungy jumping, believe me.

14 | (Laughter.)

15 | MS. COHEN: There are people who do not believe
16 | in abortion, and they have a right not to believe in
17 | abortion. When you question people or have these lists of
18 | things, is that going to in any way affect how you feel
19 | about allowing them to use thalidomide? And what if
20 | someone does need an abortion, how is that going to be
21 | dealt with?

22 | And I will ask the other question, because it
23 | has been in my mind -- two more questions actually.
24 | Thalidomide did come into this country through buying
25 | clubs. Is there any information available on what happened

1 to that use of thalidomide, in terms of teratogenicity and
2 neurotoxicity? I would like to know that.

3 And, finally, with due respect, I am sitting
4 here and I am thinking in my mind that you are going to a
5 great deal of effort. And I understand we only have
6 approximately 200 cases of leprosy a year, and that is 200
7 too many. Are you anticipating using another use of your
8 drug, and should you share it with us now so that we can
9 understand and you won't have to come back and come back
10 and come back again and maybe can encompass it all the way?

11 DR. MCGUIRE: To whom was that directed? Were
12 you directing that to one of the sponsors?

13 MS. COHEN: Yes, absolutely.

14 DR. MCGUIRE: Would anyone from Celgene like to
15 respond to that? Jerry?

16 DR. THOMAS: Hi, Steve Thomas again.

17 I'll take a first approach actually at
18 answering a very important question, Mrs. Cohen.

19 As I think we tried, or I tried, specifically
20 to point out, our company is actively, extensively
21 evaluating the use of this agent in a number of other
22 life-threatening indications. AIDS wasting is mentioned,
23 aphthous ulceration in HIV positive individuals, and graft
24 versus host disease.

25 If the efficacy and the safety of the drug in

1 | these indications is clearly established, we would intend
2 | to provide information in a range of NDA submissions,
3 | which, again, would fall to FDA and other committees
4 | actually to evaluate.

5 | How the drug is used is handled through,
6 | initially, the labeling of the compound and is quite
7 | clearly legislated for and directed under the regulations
8 | and the FDA. Our company is only able to make our compound
9 | available under the directions that we receive actually
10 | from FDA.

11 | We are in a position whereby we think this
12 | compound may have a variety of uses in a range of
13 | indications. Each of the risk-versus-benefit equations has
14 | to be established independently in each of those
15 | indications.

16 | I wonder if actually Bruce Williams would like
17 | to add anything?

18 | MR. WILLIAMS: No, except that, again, the
19 | proposal that we have made for the distribution system, in
20 | fact, was carefully considered because of the knowledge
21 | that usage might occur in other areas while these other
22 | indications are being developed, and that if that usage
23 | were to occur, it had to be captured by the system and
24 | could not be allowed to be occurring outside of the system
25 | without monitoring and follow-up.

1 DR. MCGUIRE: The other piece of Mrs. Cohen's
2 question was, have there been any birth defects in the
3 orphan use applications or in the buyers' club usage? And
4 the sponsor may or may not know that, and perhaps the
5 agency knows that.

6 DR. THOMAS: Well, all that, obviously, our
7 company is able to work with is the information on the
8 exposure of our compound. It is clear from the information
9 that we have that that has not occurred. I don't know if
10 we have any more information from buyers' clubs at this
11 meeting.

12 MS. COHEN: Have you sought the information?

13 DR. THOMAS: Yes we have, indeed. However, I
14 would feel uncomfortable answering a question on behalf of
15 a range of agencies that I haven't had an opportunity of
16 addressing.

17 MS. COHEN: And I would be uncomfortable not to
18 know.

19 DR. THOMAS: I think that you have a perfect
20 right, actually, to ask that question. I'm not sure that
21 we can address that question right now. However, it is
22 totally possible that, over the course of the next few
23 days, we can do that.

24 DR. MCGUIRE: Let's give Dr. Woodcock a chance
25 the buyers' club question. Do you have any information on

1 | that?

2 | DR. WOODCOCK: We do not know of adverse
3 | pregnancy outcomes that have occurred as a result of the
4 | illegal distribution of thalidomide. Obviously, the
5 | reporting of even adverse events of approved drugs we know
6 | is under-reported, and it is very likely that drugs that
7 | are not being distributed in legal channels, that it would
8 | be more likely to be even more under-reported.
9 | Nevertheless, we have received no reports.

10 | DR. MCGUIRE: Dr. Mindel, do you have a
11 | question?

12 | DR. MINDEL: Yes.

13 | With drugs that aren't orphan drugs, in
14 | evaluating the data that is presented, there's a basis of
15 | what the FDA requires that is sort of in the back of my
16 | mind. I think of these two good controlled studies or is
17 | this a good multi-center study, and things like that. But
18 | this is an orphan drug, and your reviewers have said that
19 | it doesn't meet the criteria for approval. And I assume
20 | that the reason we are discussing this is because it's not
21 | expected that an orphan drug meet the criteria of a drug
22 | that isn't an orphan drug.

23 | I'd like to know, though, what are the
24 | criteria. Are there any internal criteria -- I am not
25 | aware of what they are -- by which an orphan drug is

1 | approved? And could you tell us how this data compares
2 | with, say, the last one or two orphan drugs that were
3 | approved? Were they controlled studies? Were they
4 | required?

5 | DR. WOODCOCK: Yes, the requirement in our law,
6 | in our statute, is for substantial evidence from controlled
7 | trials. In many cases, however, in diseases of very low
8 | prevalence or in other circumstances, where randomized
9 | controls are not possible or haven't been performed, we
10 | look at historically controlled data.

11 | In the literature submission, there are several
12 | control trials that are submitted that we have not had full
13 | access to the primary data, or when we went back to the
14 | primary patient records, the data were very confusing. So,
15 | those trials aren't, in themselves, totally adequate, as
16 | was revealed by the reviewers' comments.

17 | However, we have additional historically
18 | controlled data in this case. The issue always with
19 | historically controlled data is whether or not you have
20 | enough confidence in your understanding of the natural
21 | history of the disease and the response that you see in
22 | response to treatment that you can make a reliable
23 | inference that the drug is effective.

24 | So, we have approved quite a number of drugs on
25 | the basis of very small data sets, sometimes with surrogate

1 endpoints, often with historically controlled data for rare
2 diseases. That's correct.

3 DR. MINDEL: So that you would say that the
4 data is compatible with other approved orphan drugs in the
5 past -- the quality and the caliber and the quantity of the
6 data?

7 DR. WOODCOCK: Certainly. But what we are
8 asking you is are the inferences -- are you going to advise
9 us about the reliable inference that you can make from that
10 about a treatment effect, the presence of a treatment
11 effect from those data? The fact that they are
12 historically controlled or the fact that we do not have
13 access to the primary data sets are issues that we have
14 dealt with in the past, yes. They have to be taken into
15 account. They decrease the reliability of your inference.

16 And up against that might be the fact that
17 there have been multiple observations in numerous hands of
18 this treatment effect and other things that we want you to
19 take into account when you advise us.

20 DR. MCGUIRE: Thanks very much.

21 We have some other important presentations that
22 I don't want to compromise because of time. Mr. Warren, if
23 you wanted to make one last comment, then we will go to the
24 next presentation.

25 MR. WARREN: Yes, I did. And now that I have

1 | heard many presentations today, I will be making a lot more
2 | comments.

3 | My question follows up on my previous question,
4 | because I wanted that information. Can you license a drug
5 | in this country -- and, as I understand, the answer is
6 | going to be yes. Can you license a drug in this country on
7 | a condition basis, so you are licensing for leprosy? And
8 | can a mandatory restriction be put on that so it's only
9 | used for that condition? And then, should you receive the
10 | efficacy or all of the data regarding the next use, then
11 | you would license it strictly for the next use?

12 | Because we have strong concerns -- and
13 | Mrs. Cohen is the first person that has expressed it in a
14 | way that I could digest and really get into -- and that is
15 | regarding off-label. That certainly is my belief firmly.
16 | And I may be inappropriate in stating it, but, really, I
17 | think we should be dealing with the off-label issues. I
18 | really do. I think we are going a long way around.

19 | The second part is -- and I know the answer to
20 | this as well -- there have been no long-term studies
21 | conducted on our mothers, who took this drug 40 years ago,
22 | and nobody has chosen to study the long-term effects on
23 | them. Wouldn't that be useful data? Because those persons
24 | who may take it today may survive whatever illness or may
25 | live long term and never have to take thalidomide again,

1 and wouldn't we like to know what the long-term effects
2 would be on those populations?

3 And my last point, because I thought it was
4 also very important, is we have always advocated, regarding
5 abortion, is that it should be a person's choice regarding
6 that regard. But our concern comes from a different point.
7 And that is that people should not be forced to sign
8 anything that would force them to have an abortion should a
9 thalidomider be born, and that is what we call ourselves,
10 because we have some quality of life and some right to be
11 here.

12 Thank you.

13 DR. MCGUIRE: Dr. Bashaw, you had a comment?

14 DR. BASHAW: Yes. I would like to make a
15 clarification, if the committee would indulge me, about a
16 comment I brought up during my presentation with regards to
17 the drug interaction study with oral contraceptives. I
18 alluded to the fact that there are some changes going on in
19 that area and I have been asked to clarify that.

20 When the protocol that was done for thalidomide
21 was developed, it was approximately a year and a half,
22 almost two years ago. And it basically involved looking at
23 the pharmacokinetics of the various combinations -- ethinyl
24 estradiol and norethindrone and also thalidomide, and
25 looking for kinetic interactions. Obviously, there is also

1 | pharmacodynamic measures which can also be taken -- FSH,
2 | LH, and other tests which can be done.

3 | Since this protocol was initiated, there have
4 | been discussions between the Dermatology Division, with the
5 | reproductive side of the FDA, and also the Division of
6 | Biopharmaceutics, Clinical Pharmacology, looking at ways of
7 | improving the study design and making a better protocol.

8 | And that is what I was alluding to in my
9 | presentation, that, in the future, we will be coming to
10 | this committee with a different protocol for your
11 | consideration, since this committee does have a lot of
12 | experience and a lot of concern in this area, trying to
13 | look at a study design which incorporates both
14 | pharmacokinetic and pharmacodynamic measures. Because
15 | there could potentially be the possibility -- not
16 | necessarily with this drug, but there is always the
17 | possibility that while there was not a kinetic interaction,
18 | there could be dynamic interaction. And that is what we'd
19 | be most concerned about.

20 | So, that's the clarification I just wanted to
21 | offer. The study itself that was done with this NDA is
22 | acceptable, but we do have new thoughts that have come up
23 | since the study was initiated, and we are moving forward
24 | with new protocols, with others sponsors right now.

25 | DR. McGUIRE: Dennis, thanks very much.

1 Let's go to the next presentation, by Dr.
2 Cynthia Moore, on birth defects due to thalidomide
3 exposure, CDC considerations.

4 DR. MOORE: Before I begin, I would like to
5 mention that actually the most important word in the title
6 of my presentation was omitted. And that word is
7 "preventing." It goes at the beginning of the title.

8 I do want to thank you for the opportunity to
9 attend and to participate in this important meeting. The
10 Centers for Disease Control and Prevention entered this
11 arena because a major part of the Division of Birth Defects
12 and Developmental Disabilities' mission is to improve the
13 health of American children by preventing birth defects.

14 To a great extent, our division owes its
15 existence to the tragedy that was the first thalidomide
16 epidemic and we, as well as others, do not wish to see it
17 occur again.

18 In March of this year, CDC sponsored a workshop
19 in Atlanta entitled "Preventing Birth Defects Due to
20 Thalidomide Exposure." We were fortunate to have
21 participation by individuals from many different areas of
22 expertise, including our federal colleagues from the FDA
23 and NIH, many pharmaceutical companies, professional
24 practice representatives, academicians, and others.

25 The purpose of this meeting was to provide a

1 forum devoted to the discussion of the teratogenic effects
2 of thalidomide and methods to limit fetal exposure to this
3 drug should it be approved for use. This meeting was not
4 designed to develop a consensus on this issue, and no
5 attempt was made to reach one, but merely to gather
6 individual suggestions by the meeting participants.

7 Although other adverse effects of this drug are
8 known or suspected, the CDC meeting addressed only the
9 teratogenic effects. I believe we all are well aware of
10 these birth defects. We know that when this drug is used
11 by women of childbearing potential, the risk for causing
12 serious birth defects can never be lowered to zero. In
13 situations where there is indiscriminate use of the drug or
14 poor control surrounding its use, as in Brazil, infants
15 with thalidomide embryopathy are being born.

16 May I have the first slide, please?

17 This infant was born approximately two years
18 ago to a Brazilian mother who received thalidomide for
19 leprosy. He has the typical limb malformations that we see
20 associated with thalidomide exposure.

21 For the 5 patients at the Hansen's Disease
22 Center in Carville, Louisiana, who are currently receiving
23 thalidomide for treatment of ENL, the teratogenic risk is
24 small, especially since 4 are males. The risk may also be
25 lower for individuals who are buying thalidomide through

1 | buyer networks, since I understand that members of these
2 | clubs are also primarily male.

3 | Incidentally, as of yesterday, the buyers' club
4 | group in Atlanta was very active and willing to sell
5 | thalidomide.

6 | The CDC meeting considered not only the
7 | teratogenic risk for individuals with ENL, but also the
8 | risks that this approval could bring to a population of
9 | patients with other disorders for which treatment with
10 | thalidomide has given beneficial results. There isn't time
11 | to present everyone of the dozens of suggestions we heard
12 | at that March meeting. Our staff considered all of them,
13 | and extracted those which we thought would be most
14 | effective and practical in preventing fetal exposure.

15 | In the form of draft recommendations, these
16 | suggestions have gone out for comment to the meeting
17 | participants and are now under revision. I'd like to
18 | highlight some of those suggestions for you this afternoon.

19 | We noted that virtually all of the suggestions
20 | to prevent birth defects centered around the concepts of
21 | limiting the use of the drug, educating health care
22 | providers and patients about the use of the drug, and
23 | monitoring those who were using the drug. These concepts
24 | were summarized by CDC staff into these five proposed
25 | recommendations, focused mainly on women of childbearing

1 | potential.

2 | These are that patients should be suitable
3 | candidates for thalidomide. They should be educated and
4 | counseled about the teratogenicity and about contraception.
5 | The drug should be packaged and dispensed in a manner to
6 | minimize both inappropriate and inadvertent use.
7 | Prescribers and dispensers should be well-educated about
8 | thalidomide and its use. And patients should be monitored
9 | during use to reduce the risk for fetal exposure.

10 | When considering if a woman of childbearing
11 | potential is a suitable candidate for thalidomide therapy,
12 | we thought these four points were very important. The most
13 | difficult issue has been the first point listed, for it
14 | seems that most would agree with the other points -- that a
15 | prospective patient should not be pregnant at the
16 | initiation of therapy, should have access to and be a
17 | capable and effective user of birth control, and should
18 | understand the risks associated with using this drug.

19 | However, when to use the drug is the question.
20 | It was suggested at the meeting that the drug should have
21 | not only been proven to be effective for the condition, but
22 | because of the severe risk, other options -- hopefully,
23 | non-teratogenic -- should have been tried first, if
24 | available.

25 | Since approval of a drug for a specific use

1 must be based in part on its effectiveness, it was also
2 suggested by some meeting participants that the common
3 practice of off-label use of drugs be prohibited for
4 thalidomide. Again, this is controversial, but it would
5 limit exposure at least until other indications are
6 approved.

7 Patients should, of course, be counseled about
8 the teratogenicity. In all patient education activities,
9 the concepts of appropriate and pre-tested messages, with
10 post-educational knowledge assessment, are included.
11 Several meeting participants stressed the need for
12 inclusion of photographs of affected infants. And we have
13 heard that again today. The line drawing of an infant with
14 Accutane embryopathy that is included in the Roche
15 pregnancy prevention program was thought to be inadequate.

16 Also, avoiding possible fetal exposure caused
17 by sharing pills or taking left-over pills necessitates
18 counseling all patients about the teratogenicity and the
19 importance of not keeping unused pills.

20 The choice of an effective contraceptive
21 approach, particularly for individuals with a chronic
22 illness, can be a challenging effort according to our
23 OB/GYN colleagues. It was suggested that this practice be
24 limited to those providers with expertise in this area.
25 Although consistent and proper use of contraception is the

1 goal, unprotected intercourse could occur under a number of
2 circumstances. This topic also elicited many comments from
3 our meeting participants, since we proposed that emergency
4 contraception be discussed and prescribed.

5 At the very least, as one of our participants
6 suggested, female patients of childbearing potential who
7 have unprotected sexual intercourse should stop taking
8 thalidomide immediately and not resume until they have been
9 evaluated and found not to be pregnant. This same
10 suggestion would apply to women who are uncertain about the
11 effectiveness of their contraception at any point in time.

12 I would like to acknowledge Sally Cooper, from
13 PWA, who gave us this suggestion, since she so graciously
14 earlier gave up her time.

15 Packaging suggestions included labels that
16 state "causes severe birth defects" and the word
17 "thalidomide." How recognizable the word "thalidomide" is
18 to individuals in their 20s or 30s who may be patients or
19 even health care providers was not known to us, I guess
20 still is not known to us, but we have a little information
21 on that given today.

22 Other ideas such as blister packs and use of a
23 tested symbol to denote no use in pregnancy were also
24 discussed during the meeting.

25 Although we've received both positive and

1 negative feedback about these suggestions on dispensing,
2 the last two stimulate the most discussion, mainly
3 pertaining to the idea that the pharmacist would also be a
4 gatekeeper for thalidomide and in some ways serve as the
5 ultimate control over who receives the drug. This is not
6 an idea without precedent. For at least one drug,
7 Clozaril, dispensing cannot be done unless the pharmacist
8 is presented documentation of requisite laboratory results.

9 The most notable point under this heading is
10 the suggested concept that prescribers and dispensers
11 should do more than just register to obtain the privilege.
12 Education and knowledge assessments should be connected to
13 this privilege, a privilege which also could be revoked.
14 The development of specific practice guidelines by
15 professional groups was also suggested.

16 Monitoring suggestions pertain to follow-up of
17 the female patient while on therapy by her health care
18 provider and referral for specialized counseling in the
19 event of an exposed pregnancy.

20 In addition, a more global monitoring of all
21 women of childbearing potential through the establishment
22 of a prospective registry was suggested. This registry
23 would follow all women of childbearing potential on
24 thalidomide for fetal exposure and outcome of the exposed
25 pregnancies. The registry would provide information to

1 | determine the magnitude and hopefully the source of
2 | prevention failures.

3 | That is the last slide.

4 | I've given a brief overview of the suggestions
5 | from the CDC meeting Preventing Birth Defects Due to
6 | Thalidomide Exposure. As an encompassing summary, we were
7 | told that the most rigorous pregnancy prevention program
8 | yet described, the Roche pregnancy prevention program for
9 | women on Accutane, was a good starting point but not
10 | rigorous enough for a teratogen as potent as thalidomide.

11 | Evaluation of this program has shown that some
12 | women received Accutane without a pregnancy test,
13 | pregnancies did occur during therapy, and affected fetuses
14 | were aborted or went on to live birth. Unfortunately, even
15 | with a stronger program for thalidomide, some affected
16 | infants will also be born.

17 | We would like to thank all the participants in
18 | our meeting. Several of them are here today. Our Birth
19 | Defects Group at CDC is eager to further explore
20 | suggestions from the meeting and work with all parties to
21 | develop a prevention program that hopefully will assist
22 | women who receive thalidomide, their partners, and their
23 | health care providers in preventing these serious but
24 | preventable birth defects.

25 | Thank you.

1 DR. MCGUIRE: Thank you, Dr. Moore.

2 We have time for a few questions. Dr. Duvic?

3 DR. DUVIC: Thank you very much for the
4 presentation.

5 I share Dr. Bergfeld's concerns that we do not
6 know yet about fat storage and lipid solubility of this
7 drug. For etretinate, the drug can hang around in fat for
8 as long as a year. If this is the case for something like
9 thalidomide, then stopping the drug on day 1 of pregnancy
10 would have no effect. So, before we could even consider
11 using this drug in women of childbearing age, we would have
12 to have that data. And I have heard no one answer that
13 question today.

14 DR. MOORE: I agree with you. The preliminary
15 data that we looked at, which was slim, suggested that it
16 was rapidly removed from the body, but I do agree with you
17 totally that you would need to know that information.
18 Actually the drug that you mentioned may hang around for
19 many years.

20 DR. MATHEWS: In follow-up to that same point,
21 do you know if there's any epidemiologic evidence that
22 could address that question from the initial epidemic? In
23 other words, women who took the drug prior to pregnancy at
24 varying intervals of time prior to becoming pregnant and
25 whether there were any detectable cases attributable to

1 that type of exposure.

2 DR. MOORE: I don't know that for certain. I
3 have not read any account of that in the considerable
4 literature that there is, but a lot of it is -- how shall
5 we say -- cases that were gone back and looked at much
6 later, and whether or not there is ability to pull out
7 individuals who may have been exposed in this manner, I
8 don't know from those older papers. I don't know if
9 there's anyone else here in the audience that could answer
10 that question. I really can't.

11 DR. McGUIRE: I think we have seen data
12 indicating that there is a particular period, after
13 implantation, of peak sensitivity. Of course, my memory is
14 not good enough to remember where I saw it or read it.

15 Does the sponsor know about that? Did I read
16 it in the black book? Okay.

17 DR. MOORE: That is true, absolutely true, that
18 there is a critical period. But I think what the
19 questioner was talking about is women who stopped use prior
20 to this critical period and would the drug hang around long
21 enough in some body tissue to actually cause a problem.

22 DR. THOMAS: It's actually Steve Thomas again.

23 It is a valid question. The information that
24 is highly consistent in the literature across humans and
25 other species is that there is a narrow window which has

1 | been described after implantation where the fetus is
2 | apparently highly susceptible to harm.

3 | Yes, it is important to note that if there were
4 | a problem associated actually with the drug hanging around
5 | longer than would otherwise normally be expected from the
6 | data that we have actually presented and also from the
7 | extensive literature, we would not be able to make a
8 | comment on that window because that window would actually
9 | be highly susceptible to a variability of the drug leaching
10 | from fat stores, which we just have not seen.

11 | It is a very valid question. There's nothing
12 | in the literature that we are aware of -- and we have
13 | looked at all of it -- that would indicate it is a problem.
14 | I think that's all I can say on that issue.

15 | DR. MCGUIRE: Dr. Kilpatrick had a question.

16 | DR. KILPATRICK: Actually, sir, two questions
17 | of Dr. Moore.

18 | A long time ago I was involved in a WHO
19 | international study of fetal abnormalities. I don't think
20 | this occurs, but there's no such thing as registration in
21 | the United States of fetal abnormalities, still births and
22 | live births? Can we come at it from another direction and
23 | come at cases and go back and look? But is there such a
24 | registration or any demographic requirement?

25 | DR. MOORE: Well, there are multiple birth

1 defects surveillance systems that exist in the United
2 States, and there is one in Atlanta that is run by CDC in
3 the metropolitan area.

4 I think this would be a very difficult question
5 to answer using that mechanism when you may be talking
6 about a difference of a few days. The critical period that
7 we're talking about is the period of organogenesis, and
8 it's a critical period for exposure to any teratogen.

9 I would like to add that we really don't, I
10 think, have the answer to whether there are problems with
11 later exposure after the organs have formed, but the
12 central nervous system is still developing in a fetus up to
13 term. There have been some reports of children with
14 functional problems such as mental retardation. At present
15 those babies I believe have had other birth defects that
16 were fairly typical of thalidomide embryopathy. In babies
17 who had just these functional problems alone, it was
18 questioned whether or not it was due to thalidomide.

19 But I'm not totally comfortable saying that
20 just using thalidomide in that early period of
21 organogenesis is the only time that you could do harm to a
22 developing fetus.

23 DR. KILPATRICK: I should perhaps explain why
24 the question arose. I'm thinking in terms of perhaps
25 designing something like a case controlled study going from

1 cases back to see what the risk factors were and whether
2 thalidomide is involved because we've heard that other
3 prospective studies may not be determining of whether
4 thalidomide causes fetal effects. But I thank you for
5 that.

6 The second question is concerned with
7 transmission. The general public has been alerted to the
8 transmission of HIV in a variety of ways, in fact perhaps
9 overly sensitized to it. I've been struck by the fact that
10 thalidomide is excreted in urine. Is it excreted in
11 saliva? We've heard about it's unknown as to whether sperm
12 contains thalidomide, and breast milk is uncertain. Can
13 you make any observations about the accidental transmission
14 of thalidomide to childbearing women?

15 DR. MOORE: I cannot. I don't know if anyone
16 from Celgene --

17 DR. MCGUIRE: Dr. Bashaw had a question. Maybe
18 he also can help answer one of your questions.

19 DR. BASHAW: Actually it was a comment
20 regarding the time that thalidomide would remain in the
21 body. It's sort of another way to look at it. We looked
22 at the solubility of thalidomide looking for oral
23 solutions, and in water has a very poor water solubility,
24 but its alcohol solubility is equally almost as poor. It
25 has really got a unique solubility profile. About the best

1 | thing it's soluble in is only DMSO which sort of
2 | incorporates both polar and nonpolar solubilities.

3 | So, in terms of would thalidomide itself
4 | readily go into fat tissues, based on its chemical nature,
5 | most likely it would not, and when you look at the
6 | hydrolysis products, again the structures that I presented
7 | in my review, the theoretical ones for metabolites, again,
8 | they all contain carbonyls and carboxylic acid groups which
9 | would put it more to the polar side where it would be in
10 | the body water.

11 | Although it's not a definitive answer, I don't
12 | think you'd have the same magnitude problem as you have
13 | with Psoriatain or acitretin or the isotretinoins. Nothing
14 | like that. There may be some deposition, but I don't
15 | believe it's very major based on the solubility information
16 | we have right now.

17 | DR. MCGUIRE: Dennis, can you speak to
18 | excretion in milk or presence in semen, saliva?

19 | DR. BASHAW: I can only speculate. We have not
20 | collected any data on it. It's probably secreted in
21 | saliva. As for breast milk, as for semen, because of the
22 | protein contents there and their fat makeup, especially in
23 | breast milk, I really would not want to comment with any
24 | degree of certainty on those. Like I said, its solubility
25 | is rather unusual. It potentially could get ion trapped,

1 | but I really wouldn't want to speculate beyond that.

2 | DR. McGUIRE: But it could be measured.

3 | DR. BASHAW: Yes. Oh, it certainly could be.

4 | The analytical methodology I believe exists.

5 | DR. McGUIRE: Are there other questions for Dr.
6 | Moore? Yes, Dr. Orkin.

7 | DR. ORKIN: It's interesting that Dr. Moore
8 | suggested that there may be some other abnormalities later
9 | on in the pregnancy that are not typical of thalidomide as
10 | we recognize it.

11 | Along that line, I thought that Mr. Warren's
12 | comment about the fact that the second generation in the
13 | mothers is not known. I wonder is there any data -- and I
14 | think the answer is probably no, but it would still be
15 | interesting to know, important to know if there were other
16 | children of those mothers who had some abnormalities that
17 | were not of the typical form but were atypical.

18 | DR. McGUIRE: In November, Dr. Lammer had a lot
19 | of information concerning the etretinate children.

20 | Mr. Warren, did you have a comment?

21 | MR. WARREN: I actually had a question because
22 | you brought up an interesting point, a speculation for us.
23 | When we were evaluated as thalidomiders -- that's what we
24 | call ourselves -- way back then, we could pinpoint to the
25 | day when our mothers had ingested the drug. From

1 | standpoint from all of our information, those that survived
2 | are a result of the first trimester in this highly
3 | sensitive period, but we've always suspected that it was
4 | possible that it would be at least into the early second
5 | trimester or possibly throughout the pregnancy. I'd be
6 | really curious if anybody had any information about that.

7 | DR. MOORE: Well, I'm not the first person
8 | surely to suggest that there could be other problems in
9 | addition to structural birth defects. But in order for the
10 | structural birth defects to occur, that exposure would be
11 | early in the first trimester during organogenesis, but I
12 | really can't speculate. I think it's an unknown to us if
13 | anything later in pregnancy occurs.

14 | MR. WARREN: I just wanted to follow up on that
15 | because we've always believed that there were perhaps other
16 | thalidomiders born that may have been smaller babies
17 | because maybe it was during the growth process or with
18 | other not necessarily phocomelic disabilities, that people
19 | had not recognized that their disabilities could have been
20 | a result of thalidomide, just to qualify my question,
21 | because nobody really knows. Those of us that manifested
22 | the physical disability were pretty much pronounced
23 | thalidomiders. It was a gray area, so the rest of the
24 | population who may have had disabled children at that time,
25 | we may never be aware of whether there are more

1 | thalidomiders out there than we're currently aware of now.

2 | DR. MOORE: There are multiple outcomes that
3 | can be looked at, including birth weight, growth, the
4 | functional parameters I was talking about, even whether or
5 | not there's an excess of fetal death, and all those
6 | reproductive outcomes can be looked at with different
7 | exposures. But I'm not aware of really good data on this
8 | for thalidomide.

9 | DR. MCGUIRE: Dr. Simmons-O'Brien has a
10 | question.

11 | DR. SIMMONS-O'BRIEN: Well, actually it's a
12 | comment. Having reviewed a significant portion of the
13 | literature on thalidomide, I believe -- and I'm not certain
14 | if Dr. Holmes is still here, but I believe he's an author
15 | on a paper that is a very nice paper talking about what
16 | have we learned from the embryopathy.

17 | Geneticists have gone back and have looked at
18 | the cases, some of the cases in Europe and here in the
19 | United States, and have shown that the actual syndrome goes
20 | far beyond phocomelia. There are children who were born
21 | without ears, anotia. I believe that actually might have
22 | been the first retrospective case of a worker who worked in
23 | the Gruenthal plant who gave thalidomide to his pregnant
24 | wife and had a daughter who was born without ears. So, the
25 | actual syndrome can encompass many clinical presentations,

1 pelvic girdle abnormalities.

2 But in the same breath, the paper also stated
3 that there are numerous medications that are also used that
4 can cause similar type of defects, as well as some later
5 discovered genetic syndromes, and Holt-Oram being one of
6 them by Victor McCusik. So, in the literature this is
7 discussed.

8 DR. MOORE: I agree with you completely. There
9 are several authors and teratologists who have gone back
10 and discussed that. It's a reality in birth defects that a
11 complete evaluation is needed of a child who has structural
12 birth defects before a cause is placed on that occurrence.

13 DR. MCGUIRE: Dr. Moore, thank you. I think
14 we'll go on to the last presentation.

15 DR. MOORE: Thank you.

16 DR. MCGUIRE: Colin Crawford will speak on
17 thalidomide neurotoxicity which, by the way, was a subject
18 dealt with in some detail at our November meeting.

19 DR. CRAWFORD: Thank you very much for asking
20 me to talk. I'm Colin Crawford. I trained in New Zealand
21 and then I came to the U.K. to do postgraduate work, and
22 then in 1966 I went to Africa to work with leprosy
23 patients, both clinical management and field work, firstly
24 in northern Nigeria and then in Tanzania. So, I had about
25 four and a half years of experience with leprosy patients.

1 Now, thalidomide neuropathy is a very serious
2 complication that can lead to severe sensory loss which may
3 be irreversible. In fact, two British pharmacologists,
4 Darcy and Griffin, have stated, referring to the events of
5 1960 and 1961, that this side effect alone was severe
6 enough to cause the demise of the drug, even if the
7 teratogenic disaster had not supervened.

8 The teratogenic effects can be avoided by not
9 giving the drug to women of reproductive age, but anybody
10 who takes the drug is liable to develop a neuropathy.

11 If we can have the first slide please. We can
12 look at the clinical features. It's initially a sensory
13 neuropathy. All modalities can be affected, but an
14 important point is there may be a selective loss of
15 superficial pain and temperatures which can be confused
16 with leprous neuropathy.

17 The dying-back neuropathy which means the main
18 involvement is in the distal extremities of the lower
19 limbs, symmetrical nature, and common symptoms are burning
20 pain in the feet and cramp-like pains in the calf. The
21 knee and ankle reflexes may be diminished, but if there's
22 pyramidal tract involvement, they may be increased with
23 extensive plantar responses. As a late stage, if the drug
24 is continued, there is a characteristic paralysis of the
25 proximal muscles.

1 The pathology is it's an axonal neuropathy
2 first affecting sensory myelinated fibers, can be detected
3 by sural nerve biopsy, and unmyelinated fibers appear to be
4 unaffected.

5 You can see on the right here the normal
6 control of vesicular sural nerve biopsy and the great loss
7 of myelinated fibers in a patient who has taken
8 thalidomide.

9 The control values show that there's a bimodal
10 distribution, with the larger diameter fibers in the 10 to
11 20 micron range. In these 2 patients who have been given
12 thalidomide, there is a great loss of myelinated fibers,
13 and in some cases a shift to the left, implying some degree
14 of regeneration of smaller caliber fibers.

15 The third measure to detect the neuropathy --
16 you may not be able to read this too well. It's an axonal
17 neuropathy, so the most sensitive test is sensory nerve
18 action potentials, and nerve conduction studies are usually
19 normal.

20 In this French study, which was published in
21 1986, for non-leprosy disorders, mainly dermatological, the
22 control values are 16 here and the sural nerve action
23 potential was grossly diminished in many patients. Some
24 were normal. These were the symptoms that the patient got.

25 On the right here is the cumulative dose given

1 over several months. You can see 1 patient developed a
2 neuropathy after only 9 grams. That would be 100
3 milligrams over 3 months.

4 Now, other features of the drug. The frequency
5 in non-leprosy disorders is reported as at least 21 percent
6 if sensory nerve action potentials are carried out to
7 detect subclinical neuropathy.

8 There is no minimum dose below which it is safe
9 to give the drug.

10 It's not due to hypersensitivity.

11 One study on the genetic factors did not seem
12 to be significant.

13 Although these things may be significant, the
14 latest papers suggest they may not be able to predict a
15 neuropathy.

16 Really, in conclusion, the chances of
17 developing a neuropathy are probably unpredictable.

18 The prognosis. If the drug is stopped, motor
19 and pyramidal involvement is reversible. However, the
20 sensory loss is permanent in 50 percent of the patients,
21 even years after stopping the drug.

22 One of the things Dr. LaQuesne pointed out is
23 this persistent painful paraesthesiae which were painful
24 and disabling and were the most distressing thing about the
25 effect of the drug.

1 Now, when we come to leprosy -- and you've
2 heard about the literature -- neither or any of the
3 clinical, pathological, or electrophysiological studies
4 have been carried out in leprosy patients with erythema
5 nodosum.

6 That's not a very good picture, but you've seen
7 one before. The erythema nodosum, or ENL, painful nodules
8 under the skin. They're generalized.

9 I think an important point that Dr. Wilkin made
10 is that we should consider the skin manifestations, and I
11 would add to that the rise in temperature which these
12 patients have. There have been a lot of comments on the
13 orchitis, the iritis, the arthritis, the nephritis, the
14 amyloidosis, but personally I did not have the facilities
15 to observe all these things. But certainly they're not,
16 from a quantitative point of view, sufficient to run
17 clinical trials and to test the efficacy of thalidomide.

18 Now, my own experience with patients with ENL,
19 14 patients: 7 in northern Nigeria and 7 in Tanzania. The
20 important point is that on clinical neurological
21 examination, 10 had no clinical signs of sensory loss due
22 to the leprosy. Therefore, by giving thalidomide, it is
23 possible to inflict permanent nerve damage on a leprosy
24 patient who would have not developed this as a result of
25 the disease.

1 4 of these had sensory loss. 2 were severe.
2 One had a trophic ulcer, another had mutilation of the
3 extremities.

4 Now, when we compare thalidomide and leprous
5 neuropathy, there are similarities, as I've pointed out.
6 In thalidomide, the sensory loss may be confined to
7 superficial sensory modalities, and the distribution may be
8 similar, being mainly distal and shading off proximally.

9 Differences are the burning pain in the feet,
10 which I had not observed and it's not recorded in the
11 literature, or cramp-like pains in the calf in 16 out of 22
12 patients, not present there.

13 Some patients may develop ataxia with
14 thalidomide. It's not present in there.

15 The reflexes are always preserved in leprous
16 neuropathy, but there may be loss but in under 50 percent.

17 Then if the drug is continued, distinctive
18 proximal muscle paralysis which is not present in leprosy.

19 So, the most important observation is the
20 clinical neurological examination before thalidomide is
21 administered, and we have no details of patients with ENL
22 of what that is. And any deterioration over weeks or
23 months must be due to the drug. Sensory loss from
24 lepromatous leprosy is very insidious and unlikely to occur
25 over a short period. We know that from Hansen's original

1 observation of the natural history of the disease.

2 Now, there have been various reasons why
3 thalidomide neuropathy has not been reported in cases with
4 ENL, and as you've heard, it's either none has been
5 reported or only less than 1 percent. One of the reasons
6 comes from Waters, that the nerves of lepromatous patients
7 are relatively insusceptible to thalidomide-induced nerve
8 damage. This is based on the preservation of reflexes in
9 leprosy patients who have received thalidomide. However,
10 they were only absent in under 50 percent from Fullerton's
11 study. They will be retained if there's pyramidal tract
12 involvement. In a review article of the original
13 thalidomide neuropathy, they weren't regarded as a useful
14 diagnostic sign.

15 And the reflexes were preserved in a patient
16 with AIDS who developed a neuropathy after taking
17 thalidomide, and the nerve biopsy in that patient showed --
18 here's the normal control -- there's a gross loss of
19 myelinated fibers in this patient.

20 Another reason put forward by Robert Hastings,
21 who had never seen a case of neuropathy, this could be the
22 disease has already -- we have no data as to what the
23 precise clinical examination there was. As I've said, in
24 my patients, 10 out of 14 didn't have clinical neurological
25 abnormalities. It's published in the Journal of

1 American --

2 And electrophysiological studies have been
3 taking place. In this recent editorial from the Lancet,
4 the agent has been used in leprosy for many years, but
5 leprosy patients treated with the drug even after careful
6 study -- and this is a reference to a letter published in
7 1969 which is on the motor conduction velocities in the
8 ulnar nerve at the elbow. While thalidomide neuropathy is
9 an axonal neuropathy, conduction studies will not be
10 affected.

11 Thalidomide neuropathy is a dying-back
12 neuropathy, so the main and severe involvement will be in
13 the distal parts of the lower limb.

14 As it's mainly sensory, the motor conduction
15 velocities are unlikely to be affected.

16 This study was carried out in 1969 only four
17 years after the drug was administered. We have had nearly
18 another 25 years to assess whether there are side effects.

19 Now, recently the United Kingdom have laid down
20 guidelines for the administration of thalidomide to
21 patients in Britain. Each patient is provided with an
22 information sheet, and on it is stated in bold letters,
23 "should you develop pins and needles, you must stop
24 thalidomide immediately." They point out in the guidelines
25 and in an accompanying article it was a common, severe, and

1 often irreversible side effect of treatment with
2 thalidomide.

3 They recommend at least one, preferably two,
4 pretreatment measurements of sensory nerve action
5 potentials in at least three nerves -- sural, median, and
6 the ulnar nerve -- and that they should be repeated at 10
7 gram increment in total dose or at six monthly intervals,
8 whichever is the smaller. A fall from the baseline of
9 greater than 40 percent should be regarded as significant
10 and the drug should be stopped. If this is done, the hope
11 is that the symptoms may -- that they may offer the best
12 hope of recovery.

13 However, if we go back to the French -- and on
14 the labeling, the label should contain a warning, "contains
15 thalidomide."

16 Now, some of you may have been the film brought
17 out by the ITV First Tuesday on the teratogenic disaster in
18 Brazil. Up till that point, the bottles containing
19 thalidomide were administered to patients in the U.K.
20 without the warning "contains thalidomide." It was only
21 after the film was shown that that was recommended.

22 On the labeling, it causes serious damage to
23 babies if taken by women during pregnancy.

24 However, there's no warning about risk of nerve
25 damage, and the U.K. law states that suppliers of a drug

1 are not legally required to provide contraindications,
2 warnings, and precautions. It is the responsibility of the
3 medical person giving the drug to explain to the patient.

4 If we go back to the electrophysiological
5 studies, this number 4 and number 9 are asterisked. These
6 were patients who developed a neuropathy with a fall in the
7 sural nerve action potential, and the drug was stopped.
8 However, there were no recovery by symptoms a year after
9 stopping the drug and the electrophysiological
10 abnormalities persisted. So, even under the optimal or
11 semi-optimal conditions, it has been impossible in those
12 two cases to prevent a neuropathy from occurring.

13 Now, I was so concerned several years ago about
14 the fact that the patients may not be warned and the risk
15 because Dr. Jacobson in a review article in this journal,
16 The Star -- the Star was published by Stanley Stein, a
17 famous Hansen's disease patient because he thought that the
18 patients with Hansen's disease should have their own view
19 and they should be able to publish their own journal. Dr.
20 Jacobson wrote an article in which he did not mention the
21 neuropathic side effects.

22 I should state that most of the textbooks in
23 America and in the U.K. of physicians who are writing about
24 the treatment of ENL do not mention the neuropathy as a
25 side effect. I'm talking about Harrison's Internal

1 Medicine, 1997, the Sissel's book, William Kelly's book,
2 and Mandel's Infectious Disease book. None of these people
3 mention neuropathy as a side effect.

4 So, much of what I've said to you was published
5 in this article. This is just a summary, but it did not
6 meet with the approval of the physicians.

7 So, in conclusion, thalidomide neuropathy has
8 not been excluded in patients for ENL. The guidelines to
9 detect thalidomide -- clinical, pathological,
10 electrophysiological -- have not been utilized in leprosy
11 patients.

12 And even if the U.K. guidelines were adopted in
13 patients with ENL, thalidomide could not really be used
14 because of the frequency of sensory disturbances. Although
15 some may not have a neuropathy, they have thickened nerves.
16 They'll bang their arms and their legs. They'll develop
17 paresthesia. So, it would be very difficult to use the
18 drug.

19 The lack of knowledge of the fundamental
20 pathological, electrophysical changes in patients with this
21 complication of leprosy would make interpretation very
22 difficult.

23 Thank you.

24 DR. McGUIRE: Thank you, Dr. Crawford.

25 We have time for questions. Dr. Bergfeld.

1 DR. BERGFELD: I have a question, Doctor. I
2 was wondering if you infer here that 100 percent of those
3 patients who were treated in the U.K. with thalidomide got
4 a peripheral neuropathy. Is that your inference here?

5 DR. CRAWFORD: No, no. I don't know what the
6 figures for neuropathy are in the U.K. I don't think
7 they've been published.

8 DR. BERGFELD: It was my impression it was
9 about 6 percent. Is that too low?

10 DR. CRAWFORD: Well, I think the French study
11 shows 21 percent at least. There's another study by
12 Harland. I think you're right about that, that it went up
13 to 50 percent in a small number of cases. Yes, I think it
14 could be as high as 50 percent.

15 DR. SIMMONS-O'BRIEN: Dr. Crawford, with your
16 experience in your particular patients, could you comment a
17 little bit on their dosages and how long they took those
18 doses. In at least the patients who did get the
19 neuropathy, did that in any way correlate with the amount
20 of drug and the length of time that it was given?

21 DR. CRAWFORD: In my patients?

22 DR. SIMMONS-O'BRIEN: The patients from
23 Tanzania --

24 DR. CRAWFORD: No, I think there have been
25 various conclusions drawn, that the cumulative, the total

1 | dose was important and the daily dose might be, but the
2 | paper from Harland referred to suggests these may not be
3 | significant features. But I don't know what the up-to-date
4 | picture is. There's certainly no minimum dose below which
5 | it's safe to give the drug.

6 | DR. McGUIRE: No more axonopathy questions.

7 | DR. KILPATRICK: If you want me to ask a
8 | question, I can ask a question.

9 | DR. McGUIRE: I'm pretty enthusiastic about it,
10 | yes.

11 | DR. KILPATRICK: Sir, in the United Kingdom I
12 | notice that you use the word "thalidomide" in your
13 | labeling. Was that deliberate or was that in avoidance of
14 | a trade name or was that how it's known there?

15 | DR. CRAWFORD: No. It is known as thalidomide.
16 | The original name was Distaval back in the 1960s when the
17 | drug came back. But as I tried to point out, up till the
18 | time of the film which was shown, the bottle just contained
19 | GC233 or something like that, and it was the director of
20 | the film, James Cutler, who pointed that out. I might say
21 | the committee didn't give him credit for bringing that to
22 | light.

23 | DR. McGUIRE: Dr. Cornblath, do you have any
24 | comments?

25 | DR. CORNBATH: I think in general we both

1 | looked at the same literature and come to the same
2 | conclusion. It would be nice to have some modern day
3 | prospective studies in these populations that clearly
4 | prospectively doing electrodiagnostic studies on people who
5 | are going to receive will prevent people from getting any
6 | neuropathy, that electrodiagnostic studies will pick up
7 | people before they have symptoms.

8 | The only curious comment that I'd make here
9 | about your own personal experience is I was surprised to
10 | see that the 4 patients who developed neuropathy that you
11 | thought was from thalidomide actually developed what we
12 | would consider neuropathy of small fibers with mutilating
13 | acropathy and trophic ulcers, something that we don't
14 | usually associate with large fiber abnormality because
15 | you've shown, as have others, that the large fibers are
16 | abnormal and the small fibers are normal. So, it's
17 | surprising that you concluded, to me at least, that the
18 | neuropathy in those 4 patients was due to their thalidomide
19 | when that was a small fiber abnormality and not a large
20 | fiber abnormality.

21 | DR. CRAWFORD: Yes. I should have made the
22 | point clear. I had never used thalidomide in my patients,
23 | and those observations were made on the leprous neuropathy.

24 | DR. McGUIRE: Well, while both of you are still
25 | here, I really need some help on this point. The sparing

1 of the Hansen's population from the peripheral neuropathy.
2 Do you think that was an artifact of finding a signal and a
3 lot of noise or do you think there really is some sparing
4 of that population?

5 DR. CORNBATH: I would agree with Dr.
6 Crawford. One of the primary problems is that the
7 electrodiagnostic studies that have been done would not
8 pick up the neuropathy that might occur in this population.
9 So, what we're left with, if we look at the literature
10 alone I believe, is clinical opinions about whether the
11 patients with ENL who take thalidomide develop these
12 typical distal symptoms in their feet. At least based on
13 the literature that I read and responses in particular to a
14 series of letters that were written I think in the Lancet
15 several years ago, experienced leprologists state they
16 don't see people taking thalidomide with leprosy who
17 develop these typical symptoms in the feet.

18 Granted, electrodiagnostic studies haven't been
19 done, but at least based on clinical data, which is I think
20 the best we have, I can't see that there's good evidence
21 either in the literature or by these people's experience
22 that the patients do. Maybe some of the other leprologists
23 who treat these patients long term could comment.

24 DR. CRAWFORD: Well, as I said, I think one of
25 the problems -- and we've heard from Dr. Yoder about the

1 current approach to leprosy is mainly a dermatological one
2 based on the current classification, and there's no
3 requirement really to conduct a clinical neurological
4 examination. I think that's something which possibly is
5 necessary to get baseline data.

6 DR. MCGUIRE: Dr. Miller, you have a question.

7 DR. MILLER: Dr. Crawford, you said that you
8 did not use thalidomide in your patients?

9 DR. CRAWFORD: No.

10 DR. MILLER: How did you treat ENL and what
11 kind of results did you get?

12 DR. CRAWFORD: In those days, we used to lower
13 the dose of dapsone. We had dapsone monotherapy and then
14 in Tanzania we had clofazimine. My opinion is -- and there
15 was current opinion -- that low doses of dapsone diminish
16 the severity of the ENL and you didn't get ulceration.
17 Provided you kept the morphological index down, being the
18 percentage of viable bacteria, the patients did fairly well
19 because ENL is not bacteriologically active. I mean,
20 there's dead bacteria but they're not active. So, if you
21 can maintain that, then I think they do quite well.

22 Some needed small doses of prednisone, 10
23 milligrams a day.

24 But in no sense was this a controlled clinical
25 trial. It was just working experience which one used among

1 the leprosy people in northern Nigeria. This is the way I
2 learnt to do it and this I found satisfactory.

3 I wasn't asked to talk about alternative
4 management. I think it's worth making the point. With
5 clofazimine, the pigmentary side effect is important.
6 However, there have been developed non-pigmentary
7 derivatives of clofazimine, which one would hope may be
8 useful as substitutes for clofazimine.

9 DR. McGUIRE: Would you like to comment?

10 DR. GELBER: Yes, I would.

11 Dr. Crawford, I just want to assure you -- I'm
12 Bob Gelber and I've treated leprosy patients in this
13 country for quite a while, most notably between 1979 and
14 1984 where in San Francisco I was taking care of about a
15 quarter of the U.S. patients. I think Dr. Rea has another
16 quarter of the patients.

17 We routinely in our center and in all of the
18 centers in the United States, on an initial basis and on an
19 annual basis, do detailed sensory testing, motor strength
20 testing using initially von Tri's hairs but now these
21 monofilaments. So, we are actually looking very closely at
22 our patients. Most of us are quite aware that the serious
23 complications of leprosy are neurologic and not
24 dermatologic.

25 I might say that in my experience, I never see

1 any major changes in those hair sensations, nor do I get an
2 awful lot of patients that complain of increasing numbness
3 or severe paresthesias. But those kinds of things are
4 often very hard to tell clinically from progressive leprous
5 disease which may be not either reaction or bacteriological
6 failure but even well-treated patients who do not have
7 bacteriological failure may have minimal deterioration.

8 But the bottom line here is that, number one,
9 we are alert to this. We do follow this and we don't see
10 it.

11 DR. MCGUIRE: Yes, please. Dr. Yoder.

12 DR. YODER: I would like to reaffirm, first of
13 all, what Dr. Gelber just said about monitoring Hansen's
14 disease patients. All patients who come to our center have
15 very detailed neurological exams and occupational therapy
16 and physical therapy with the monofilaments 100 percent,
17 and that is the standard of care in the United States in
18 our centers. Many of these testings are done by nurses in
19 other centers where they don't have the occupational and
20 physical therapists that we have.

21 We do use nerve conduction studies as well in
22 problem cases and situations where we feel we need that
23 other evaluation.

24 The other comment I would make about the
25 severity of the disease and I alluded to that this morning.

1 I have worked in Africa also in several countries, and my
2 experience was that ENL actually often was a milder
3 situation there than it is in the United States. In
4 Carville my experience is that we don't often see the
5 milder kind of cases that we did see in Africa where you
6 could use small doses of prednisone or even simple
7 analgesics. That's rare in my experience. Very few of the
8 cases we see at Carville, if we did not use thalidomide, we
9 would have to use significant doses of prednisone.
10 Clofazimine would be quite inadequate because these people
11 are ill with fever, pain, diffuse rash, and require
12 something more than simple, very mild intervention.

13 DR. McGUIRE: Thank you very much.

14 DR. CRAWFORD: I think it's really a mystery
15 why you get frequencies of 21 to 50 percent and not in
16 leprosy.

17 But the other point I think is that sensory
18 nerve action potentials, to my knowledge, haven't been
19 done, and this, being an axonal neuropathy, is the most
20 critical test.

21 If the U.K. guidelines are considered and this
22 is what they recommend, this is going to prove extremely
23 difficult in leprosy patients because we have no baseline
24 information about what sensory nerve action potentials are
25 in patients with ENL and how you monitor them.

1 DR. MCGUIRE: Mr. Warren.

2 MR. WARREN: I actually appreciate being a part
3 of the topic. We've always been concerned ourselves that
4 we thought that there should be a lot more warnings
5 regarding the potential for nerve damage and neuropathy.

6 But my question is -- because we are concerned
7 also about the off-loading, if you will, off-labeling, my
8 concern is then, from what I'm understanding here, in Great
9 Britain they're not warning regarding nerve damage or any
10 potential for neuropathy on the labeling or in any of their
11 literature? Is that true?

12 DR. CRAWFORD: No. They are well aware of the
13 neuropathy. It's just an anomaly about U.K. law that it's
14 not a responsibility of the manufacturer to mention it in
15 the labeling. According to the chairman of the Committee
16 on the Safety of Medicines, the law would have to be
17 changed. I think that's wrong, but one would hope that
18 with all the trouble, that the manufacturer would volunteer
19 to mention the side effects.

20 MR. WARREN: So, who does it fall to? Is it
21 the doctor's responsibility then before prescribing, and is
22 that carried through? Do you have any -- I just feel like
23 there's a piece missing.

24 DR. CRAWFORD: We don't know what their
25 position is. I don't treat any patients in the U.K., so I

1 don't know what their attitude is.

2 DR. McGUIRE: Dr. Crawford, I'm about ready to
3 make a few closing announcements. Thank you very much.

4 I'd like to thank the people who spoke in the
5 public discussion, and I'd like to thank the members of the
6 agency and the sponsor for your precise and clear
7 explanations of what we're here about.

8 This room will be locked tonight if any members
9 of the committee wish to leave their books here.

10 I request that all of you take your questions
11 home with you this evening and have a look at them. It
12 will make tomorrow go a little easier.

13 I think that's about it for me, and the
14 Executive Secretary has some remarks.

15 MS. RILEY: Thank you. This is for the members
16 only. There is an address verification sheet in your
17 folder. If it could be filled out and returned to me by
18 sometime tomorrow, that would be great. There's an item
19 missing, though. If you have an e-mail address, I would
20 really appreciate you adding that to the list. Thank you.

21 DR. McGUIRE: We are adjourned and will convene
22 in this room at 8:30 tomorrow morning.

23 (Whereupon, at 5:00 p.m., the committee was
24 recessed, to reconvene at 8:30 a.m., Friday, September 5,
25 1997.)