Food and Drug Administration
Center for Drug Evaluation and Research

SUMMARY MINUTES OF THE DERMATOLOGIC & OPHTHALMIC DRUGS ADVISORY COMMITTEE

MEETING # 44

Thalidomide Issues

November 7 and 8, 1996
Quality Suites, Rockville, MD

Members Present
Dermatologic & Ophthalmic Drugs Advisory Committee

Joseph McGuire, Jr., M.D.,Chairman
Janice Dutcher, M.D. (Oncology Drugs Committee)
Susan Cohen, B.S., Consumer Representative
Ken Hashimoto, M.D.
S. James Kilpatrick, Jr., Ph.D.
W. Christopher Mathews, M.D. (Antiviral Drugs Committee)
Joel Mindel, M.D.
Milton Orkin, M.D.
Frank Parker, M.D.
E. William Rosenberg, M.D.

Members Not Present

Lynn Drake, M.D.
Madeleine Duvic, M.D.
Sadeer Hannush, M.D.
Johanna Seddon, M.D.
Eduardo Tschen, M.D.
M. Roy Wilson, M.D.

FDA Consultants & Guest Speakers

Wilma Bergfeld, M.D.
John J. DiGiovanna, M.D.
H.H. Schaumburg, M.D.
David Simpson, M.D.
David H. Cornblath, M.D.

FDA Participants

Mary Pendergast, Esq
Michael Weintraub, M.D.
Jonathan Wilkin, M.D.
Kathryn O'Connell, M.D.
Brenda Vaughan, MD
Frances Kelsey, M.D.

Executive Secretary

Tracy Riley

These summary minutes for the November 7 and 8, 1996, meeting of the Dermatologic & Ophthalmic Drugs Advisory Committee were approved on 19 July 1999.

I certify that I attended the November 7 and 8, 1996, Committee meeting and that these minutes accurately reflect what transpired.

Tracy Riley
Executive Secretary

Joseph McGuire, Jr., M.D.
Chairperson

November 7 - Closed Session

8:30 - 1:00 **Closed Session**

The Committee discussed trade secret and/or confidential commercial information relevant to pending new drug applications and investigational new drugs. This portion of the meeting was closed to permit discussion of this information as per 5 U.S.C. 522b(c)(4).

November 7, 1996 - Open Session

The purpose of this meeting was to discuss the teratogenicity and neurotoxicity issues regarding the use of thalidomide in treatment of several indications. The Committee members had been supplied with a background briefing book from the FDA. The meeting was held in the Main Ballroom of the Quality Suites Hotel, Rockville, Maryland. The meeting was attended by approximately 150 persons.

At 1:00 p.m., The Chairman, Joseph McGuire, Jr., M.D., called the meeting to order and the meeting participants introduced themselves. After the Conflict of Interest Statement was read by Tracy Riley, Executive Secretary, Dr. McGuire introduced the open public hearing speaker. Presentations commenced when the public hearing speakers were finished.

FDA Introductory Remarks - Mary Pendergast, Esq.

Ms. Pendergast outlined the history of and present basis for the reexamination of thalidomide for legitimate prescription use in the U.S.A. The drug was available for a long time under a treatment Investigational New Drug Application through the Hansen's Disease Center, and showed promise for being effective in treating other diseases. But, it had also been used in an illegal, uncontrolled, underground fashion for myriad other conditions. Well-researched studies to determine safe and effective treatment indications, using reliably standardized drug product in appropriate patients, had not been done. There was no effective system of controls in place to prevent tragic birth defects. Ms Pendergast stated that in November, 1995, the Agency urged manufacturers of thalidomide to seek approval for this drug, because "thalidomide has the capacity to cure". She outlined efforts to collect usable data retrospectively and encouraged the committee to evaluate and critique proposed controls on use and distribution.

FDA Introductory Remarks - Frances Kelsey, M.D.

Dr. Kelsey gave the early history of thalidomide and the tragedy of the many affected babies worldwide that was largely avoided in the United States due to her

concerns about neurotoxicity. Reports ot the teratogenic effects of thalidomide surfaced before these concerns had been fully addressed, preventing the drug receiving approval for marketing in this country.

Presentations by Invited Experts -

Neurotoxicity of drugs & neurologic assessments: H.H. Schaumburg, M.D

Peripheral neuropathies associated with AIDS and Retroviral Drugs: David Simpson, M.D.

Thalidomide neuropathies: a review of the literature:David H. Cornblath, M.D.

Presentation of questions and open committee discussion:

QUESTIONS

I. Thalidomide Neurotoxicity Identification - Can thalidomide neurotoxicity be distinguished in the individual patient from neuropathy due to either underlying disease, such as lepromatous leprosy, or concurrent or previous exposure to neurotoxic drugs?

II. Thalidomide Neurotoxicity Risk- Is thalidomide neurotoxicity more likely to occur or be severe in patients exposed to thalidomide because of neuropathy due to underlying disease or concurrent or previous exposure to neurotoxic drugs?

III. Thalidomide Neurotoxicity Assessment

1. Is a clinical neurological examination sufficient for testing, both pretreatment and during or after treatment? If not, what additional assessments should be performed, such as recording sensory nerve action potentials (electrophysiologic testing)?

2. How frequently should neurotoxicity assessments be performed in the asymptomatic patient taking thalidomide?

In general, drug-induced neuropathy correlates better with peak dose than with cumulative dose. Continuing the neurotoxic drug after the first signs and symptoms of neuropathy can lead to irreversible changes. Even with discontinuation of the neurotoxic drug, there may be progression of the signs and symptoms of neuropathy, a phenomenon known as "coasting". Thus, the three presenting experts made a strong case for discontinuing thalidomide on the first appearance of a sign or symptom of distal sensory polyneuropathy.

The AC and the expert neurologists concluded that in some circumstances thalidomide neurotoxicity could be reliably and specifically identified. If thalidomide is given to a person with a nonprogressive, established neuropathy due to lepromatous leprosy, any increase in the indices of neuropathy can be attributed to thalidomide. Likewise, if thalidomide is given to a person with a stabile neuropathy from a previously discontinued neurotoxic drug, any increase in the indices of neuropathy can be attributed to the thalidomide. In contrast, if thalidomide is given concurrently with another neurotoxic drug, an increase in indices of neuropathy cannot be attributed specifically to thalidomide.

The AC and the expert neurologists concluded that neurotoxicity might occur more often or be more severe when thalidomide is given to patients with lepromatous leprosy or taking neurotoxic drugs. The risk for thalidomide neurotoxicity was possibly increased in patients with lepromatous leprosy and probably increased when thalidomide was used concurrently with or subsequent to another neurotoxic drug.

The AC and the expert neurologists concluded that SAFETY in clinical trials during the pharmaceutical development of thalidomide could be addressed by non-neurologists and without special electrophysiologic examinations, using directed clinical assessment. However, the neurologists recommended electrophysiologic studies along with other assessment methods in at least one clinical trial in which subjects neither had an underlying neuropathic disease nor had been taking neurotoxic drugs. Such a study could be part of another trial and would provide more information about the identification, risk, and assessment of thalidomide toxicity.

November 8, 1996 - Open Session

The Chairman, Joseph McGuire, Jr., M.D., called the meeting to order and the meeting participants introduced themselves. After the Conflict of Interest Statement was read by Tracy Riley, Executive Secretary, Dr. McGuire introduced the open public hearing speakers. Scientific presentation of the open session began once the last open hearing participant spoke..

Thalidomide Teratology and Pregnancy Prevention

Introductory Remarks - Women in Clinical Trials - Ruth Merkatz, Ph.D., RN
FDA Senior Advisor the Commissioner, Women's Health

Gestational Development and Effects of Thalidomide - Barbara Hill, Ph.D.
FDA Division of Dermatologic and Dental Drug Products

Contraceptive Effectiveness - Dr. Elizabeth Raymond, MD, MPH, Family Health International

Accutane Pregnancy Prevention Program - Robert Armstrong, MD, Roche Laboratories

Use of Birth Defects Surveillance Data to Detect Thalidomide-Induced Embryopathy - J. David Erickson, DDS, MPH, Ph.D., Center for Disease Control and Prevention

Presentation of questions and committee discussion:

QUESTION:

The critical issue was the identification of pregnancy prevention measures that would be sufficient for women of childbearing potential taking thalidomide. The AC recommended informed consent for all users of thalidomide so that drug sharing would be avoided. The AC advocated requiring women of childbearing potential to use birth control. Some advocated chemical (temporary) sterilization, specifically.

The AC also advocated restricted distribution of the drug. The Accutane Pregnancy Prevention Program was seen by the AC as insufficient for thalidomide. Although the teratogenic risks for isotretinoin and thalidomide are comparable and the likelihood of sexual activity among those prescribed isotretinoin is greater, rational clinical pharmacology was not the only standard considered in the Committee's deliberations. Since the Agency's activities are determined not only by science but also by societal values, the asymmetry in risk assessment between isotretinoin and thalidomide should be received as an important signal and not dismissed as an anomaly. Regular pregnancy testing, as advocated in the Accutane Pregnancy Prevention Program, does not prevent pregnancy. It can only identify the pregnancy early. Therefore, any control program for thalidomide should effectively ensure that no pregnancy occurs while a patient is taking the drug.

Other related comments and suggestions emerging during this session included:

1. Use the generic name (thalidomide) every place the tradename is used.
2. All packaging materials must have warnings in bold type.
3. Women who participate in thalidomide trials should first "demonstrate" ability for pregnancy prevention measures and ability to keep birth control-related health care appointments.
4. Approve a unit dose packaging that requires frequent (and controlled) refills for any extended use.
5. Place a graphic picture of thalidomide birth defects in all packaging and labeling.
6. Create educational materials for physicians and pharmacists.
7. "Synovir" would be inappropriate trade name - too similar to the antiviral drugs.

Action Items for FDA:

1. Meet internally and then communicate with Celgene to clarify:
   a ENL lesions vs. ENL syndrome
   b. Monotherapy vs. adjunctive therapy

2 Reconsider restricted distribution for thalidomide.

3. Identify the level of success and the actual mechanisms of the Accutane Pregnancy Prevention Program.

Questions raised during the discussions:

1. What does thalidomide "cure"? Or does it only "control" immunologically-mediated processes?

2. What is the minimum standard Celgene must meet to qualify under the provisions of Subpart E, Open Protocols for Investigations (21 CFR §316.40, treatment use of a designated orphan drug)?

3. How would restricted distribution affect isotretinoin, etretinate, and acitretin?

After thanking all of the participants, Dr. McGuire adjourned the meeting at 12:30 p.m.

Verbatim transcripts of this meeting are available on the FDA Website, www.FDA.GOV.