CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-785

Correspondence

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
Tel 908-271-1001
Fax 908-271-4184

11 May 1998

Michael Weintraub, M.D.
Director, Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Re: NDA 20-785
THALOMID™ (thalidomide) Capsules
Amendment to Pending Application
Serial No.: 050
CONFIDENTIAL
Study E-003/P Interim Safety Report
April 1998

Dear Dr. Weintraub:

Please find enclosed the interim safety report for the ongoing study, Study E-003/P. Relative to the most recent report, data for one new patient, P19, have been added. This report has also been submitted to IND 48, 177.

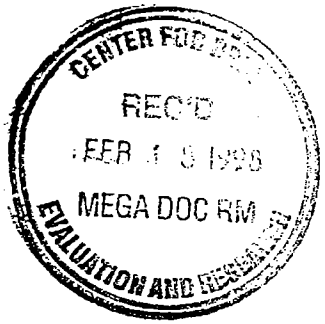
Please do not hesitate to call me with any questions or comments.

Sincerely,

Steve Thomas, Ph.D.
Vice President, Pharmaceutical Development

cc: Mary Jane Walling (desk copy)

Celgene



18 February 1998

Michael Weintraub, M.D.
Director, Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Re: NDA 20-785
THALOMID™ (thalidomide) Capsules
Amendment to Pending Application
Serial No.: 043
Updated Integrated Summary of Safety
CONFIDENTIAL

Dear Dr. Weintraub:

Please find enclosed the current update of the Integrated Summary of Safety for Thalomid™ (thalidomide, NDA 20-785). Many of the supporting documents for Celgene Corporation-sponsored studies have been previously submitted. The interim safety report for Study E-003/P was submitted 23 December 1997 (Serial No. 031), tables and listings for Studies E-001 and pooled W-001/W-002 were submitted 2 January 1998 (Serial No. 033), and the clinical pharmacology section was submitted 14 January 1998 (Serial No. 040). In addition to these previously submitted materials, other sources of safety data have also been updated. These include non-Celgene clinical studies and compassionate use of Thalomid™, USPHS IND 11,359, and the published literature. Please note that the analysis of results for the AIDS studies is ongoing and not all copies of Case Report Forms have been received from the Contract Research Organization. Therefore, the document is considered a draft.

Please do not hesitate to contact me with any questions or comments.

Sincerely,

Steve

Steve Thomas, Ph.D.
Vice President, Pharmaceutical Development

012889

MAR 27 1998

NDA 20-785

Steve Thomas, Ph.D.
Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059

Dear Dr. Thomas:

We refer to your submission of January 26, 1998, System for Thalidomide Education and Prescribing Safety, S.T.E.P.S. in support of the above referenced application. We have the following comments, requests for clarifications and revisions, and issues of broad areas of concern:

1- We are concerned that the directions to prescribers and pharmacists are inadequate. The logistics of prescribing and dispensing thalidomide, as described on pp. 012673-012683 of the submission, are not clearly reflected in the S.T.E.P.S. folder instructions nor are they consistently described in various sections. The sections labeled 1, 2, 3 in the prescribing folder are not sufficient. A patient targeted flow chart placed on the back of the folder would help. We suggest that you also prepare an annotated flow chart for the prescribing physician, based on the process description on pages 026713-012683. The flow chart should include information on the severity of the patient's ENL and the choice of thalidomide as treatment.

2- In addition, clarification, both in the process description and in the S.T.E.P.S. program brochure, is needed in the following areas:

a) You imply in the flow chart on p. 012681, entitled "Initial Office Visit", that the prescription may be given on the first visit. However, this is not congruent with the concept of obtaining a negative pregnancy test before prescribing to women with childbearing potential.
b) Should physicians contact pharmacies in advance of prescription? How does the pharmacist verify that a physician is registered when the prescription is presented to be filled, either as a first or renewal prescription?
c) Will the pharmacist be asked to give counseling to the patient? In the letter to the pharmacist (Exhibit J), you state that "the pharmacist plays a key role in ensuring patient understanding of the risks involved with therapy". However, the other materials do not indicate that the pharmacist will be asked to give counseling. What is the role of the pharmacist in this area?

d) Is a female patient able to get a follow-up prescription filled before the result of the

monthly pregnancy test is known? A procedure should be laid out in the flow chart or other instructions to physicians.

e) Weekly pregnancy testing is required for women of childbearing potential during the first month of thalidomide use. Will women be given an entire 28 day prescription at the first visit? What procedures will you recommend for follow up with the patients to ensure compliance with repeat testing during this time period?

f) Can a prescription ever be called in? If so, what procedure should be followed?

g) Please clarify how a pharmacy can register when a patient arrives with a prescription for thalidomide (page 012677) and still meet all the registration requirements listed on page 012674. You should check over the forms to avoid errors such as, including informing all staff pharmacists of the dispensing procedure for THALOMID™.

h) The word "not" should be removed from the left side of the flow diagram on page 012683.

3- Throughout the S.T.E.P.S. and the patient informed consent, the discussion of pregnancy testing, prevention, and counseling should be identical to the language used in the package insert. The language is as follows:

4- The CME monograph provided with the S.T.E.P.S. program is considered labeling for THALOMID™. Please remove the section(s) on [redacted] from the CME Monograph. Please resubmit a final Monograph consistent with the approved text of the labeling.

5- We suggest that information on emergency contraception (E.C.) be included in the materials distributed to all prescribers. In addition, we suggest that you discuss E.C. in all the materials, including those targeted to patients, along with the general contraceptive counseling instructions.

6- In addition to the purpose of preventing teratogenesis (from the possible exposure to of thalidomide in semen), please clarify for the prescribers and patients the reason for including men in the survey. Particularly mention the harm in sharing drugs and the need to track the prescription, distribution and use of the drug.

7- Please describe consequences, and at what point they will occur, in the materials for the physician, pharmacist, or patient, of "repeated non-compliance after re-education". A standard operating procedure covering this subject would be very helpful. Please clarify the conditions under which if the pharmacy or the pharmacist would be disqualified.

8- Will prescription be limited to physicians only? If so, how would this be accomplished?

9- How will the prescribing and distribution of thalidomide be done for in-patient facilities such as hospitals, nursing homes, and hospices which often use unit-dosing? How do you see the transition to other health care providers and pharmacies being handled at discharge?

10- It is stated on the inner folder of the patient brochure that ' [ ] We recommend modifying this to ' [ ]

11- The patient information booklet states that the drug should not be used by "women who could become pregnant" (page 3). This is confusing; women on birth control can become pregnant. In addition, the direction about not drinking alcohol (page 5) should be listed as precaution or as a "guideline," not merely included as a side effect. The warning on page 10 should be changed to read if a women "receives" the drug during pregnancy. The point here is that a man can pass the drug to the women during sex. Taking the drug makes it appear that the women is ingesting the drug.

12- The patient information booklet may convey to women that using two birth control methods will prevent pregnancy. Please separate out for emphasis the statement "the only method of birth control that is 100% effective..."

13- The General Guidelines on the packet could be stated more simply, e.g., "The risk of birth defects that can occur..." could be stated as ' [ ] ' and so on for the rest of bullets.

14- What is the current status of obtaining a high quality photograph of an infant with thalidomide embryopathy for the patient booklet?

15- In the patient booklet (page 5) there is a statement that ' [illegible]

] " Since many researchers estimate the proportion of infants affected to be 100% or nearly 100%, perhaps the statement is more correctly stated as [illegible]
]

16- All answers to questions on the assessment quiz should not be "true". What is the physician to do if the questions are not answered correctly? In Appendix 2 "Readability and Comprehension of Patient Education Materials", you mention an assessment by open-ended or multiple-choice questions. Has this idea been pursued? We suggest revising question four to read, for example, [illegible]

] to clearly communicate that the drug is to be used by the patient only. When will the quiz be given? As currently structured, the patient quiz is of little value for validating knowledge. Rather it serves as a reminder whose effect is diminished by giving the informed consent and the patient brochure on the first visit. A reminder would be of little value at this visit. The quiz should be recast to measure knowledge more fully.

17- The Patient Referral Form should indicate the date of the pregnancy test.

18- What does "physically able to get pregnant" mean in item no. 1 of the Informed Consent? Would the phrase " able to get pregnant and not using the required two method of birth control" convey the meaning? We recommend that there be a place for the physician to indicate that a woman does not have child-bearing potential (e.g., post-menopausal, post hysterectomy) on the physician portion of the "public health survey".

19- The Informed Consent is available in 14 languages and is to be read to the patient in the language of her choice. A health care professional fluent in the specific language, if available would discuss other documents for knowledge assessment and follow-up in the patient's language.

20- What is the status of approval for the Slone Epidemiology Unit (SEU) survey for women under age 18?

21- Will there be educational materials for nurses and other health care providers?

22- Has the proposed distribution system been evaluated by the professional pharmacy organizations?

Listed below are questions about the Thalidomide Survey components and SEU role. Areas in the survey where errors could occur, especially since it is completed without the physician's assistance, are also listed.

23 - As currently structured, the "survey" serves too much as a data collection effort and not sufficiently as an "error prevention mechanism." Many of the questions should be recast to provide better measures of what people are doing and to provide feedback to people on how to prevent pregnancies.

24- Question 11 and Question 13- What is the course of action if a patient answers a question(s) inappropriately? For example, in Question 13, it is not clear how people with multiple sex partners would complete this question or how it could be interpreted. This question may need to apply to each partner dyad. Perhaps an SOP would be helpful. The SOP should determine what pattern(s) of answers triggers a specific follow-up. The follow-up should also be included as part of the SOP.

25- Question 15 - Will patients understand the terms listed? The table to be checked off is confusing and the time spans are not contiguous. The last response option (1 year or more) is in conflict with the question "In the past year, how long have you been using each current method?" Please clarify. In addition, it is not clear how this question should be answered for methods that are not used on a continuing basis (e.g., condoms, rhythm method, abstinence). The question(s) should focus on the particular knowledge and practices during the most recent time period and attempt to spot any "system" breakdowns. For example, there should be questions about any deviations between planned and actual behavior (i.e., what types of birth control measures were planned and what were used during each of the sexual encounters during the previous one (for women) or three (for men) months. If, after counseling, people are not following through with planned behavior, this could be a sign that there is an impending problem that may need to be addressed by the patient. Generally, this survey should be a means of attesting to the labeled direction that the drug should only be provided to people who are reliable in understanding and carrying out instructions.

26- On page 012851 (page 6 of SEU proposal) paragraph 1 states [

] We assume that the definition of not using contraception includes not using two forms of protection. Therefore if patients were not using a highly effective method and a barrier method, would they be contacted?

27- How would SEU evaluate and respond to inconsistency with answers to previous questions on contraception. In some instances, a change in contraception practice is reasonable (i.e., birth control pills changed to Norplant). How will SEU verify that the patient is really changing contraception methods and not simply misunderstanding the questions? In other cases, a change in contraception practice is not reasonable. For example, a woman originally notes that she "had a hysterectomy", but now does not record that fact. The original interpretation would

have been that other forms of contraception were not necessary, but now at least two are required. How would SEU handle such situations?

28- An independent advisory board is mentioned on page 012670. What is the intended makeup of this board? Will the membership include representatives from the professional pharmacy organizations, academia, federal government, consumers?

29- What is the difference in the intended audience for the letters in Exhibits A and B, the "Dear Doctor Letters"? Several of the letters make the claim such that [ ] Please delete these statements. Statements about the recommendations of the World Health Organization regarding thalidomide as the treatment of choice are more accurate. Please revise the documents appropriately.

30- Check the document for typographical errors. For example, "used" should replace "sued" in the paragraph on confidentiality in the Thalidomide Survey Agreement.

31- Exhibit G (letter accepting a physician into the *S.T.E.P.S.* Physician Registry) states that a Celgene Immunology Specialist will visit each office to provide materials for patients. Is this to be done before the physician can prescribe THALOMID™?

32- Item 3 of the Informed Consent for Women is confusing. A woman is asked to agree to "either completely avoid sexual intercourse.....unless (she) abstains from sexual intercourse..." Please clarify.

33- Survey Enrollment Form/Envelope

The statement [ ]" in conjunction with the conditions listed, other than ENL, is misleading because it promotes off label use of the drug. Please revise.

34- Video Script and Story board

We suggest adding [ ]' to bullet two, "Use two methods of birth control," of the super checklist. There are no vivid images in this video. A prime purpose is to provide patients with clear and memorable reasons why they must avoid pregnancy. Footage of Thalidomide-babies might be helpful. Also, interviews with Thalidomide victims might be informative in this vein. Perhaps emergency contraception should be mentioned in the video when the patient is told to contact the doctor if contraception fails.

Because scripts and story boards often fail to account for factors associated with video production that could affect the communication of risk information (e.g. graphics and superimpositions of text, pacing and clarity of voice overs), we cannot provide final comments on the acceptability of broadcast advertisements unless we review the final taped version in its

entirety.

35- Blister Package

The claim [

] " is not accurate. As stated in the draft labeling for THALOMID™ [

] " Therefore, we suggests revising the claim to [

]

36- Patient Brochure

The presentation labeled ' [ ] ' would be misleading because it minimizes the frequency and potential severity of these adverse events. For example, you should emphasize the fact that peripheral neuropathy is a common, severe, and often irreversible side effect. In addition, the fact that patients should be examined at monthly intervals for the first three months is also important information to convey to patients. Similarly, the incidence of drowsiness associated with THALOMID™ use should be qualified as "frequent." Please revise appropriately.

37- General Comments Applicable to All Materials

Claims that suggest or otherwise imply that THALOMID™'s mechanism of action is well known and understood would be misleading. Although the proposed labeling provides a hypothesis, THALOMID™'s mechanism of action in ENL patients is unknown. For example, the formulary fact sheet states [

] Please delete or appropriately modify these claims.

Several of these materials offer [

] We anticipate that health care providers will contact Celgene to request additional information. Such requests would not be considered unsolicited, and therefore the responses to these requests would be viewed as promotional labeling, subject to the labeling provisions of the Federal Food, Drug and Cosmetic Act.

38- The program goal currently is described as ensuring that fetal exposure "occurs with the lowest possible incidence." A stronger objective would be for the program to prevent pregnancies

while women are taking THALOMID™ and ensure that exposure occurs with the lowest possible incidence. The prevention element is important because some elements of the program are too focused on measurement rather than pregnancy prevention.

If any of the monthly mailings with program information are essential, you could have a problem. For example, physicians may lose some information from one of the mailings. The material should have a place for all of the materials (e.g., a box as is used for Accutane). The monthly mailings should merely serve as reminders and not included essential pieces of the program that have not otherwise been included in the program materials that prescribers/dispensers have on file.

Does "Data base validation" mean that the names on the databases will be cross-checked for accuracy or otherwise submitted to some quality control procedure? Quality control procedures must be described.

Alternate Site Distributers (ASD) sells drugs only to compliant pharmacies. Stopping rules (i.e., when a pharmacy is considered not to be compliant) should be expressly noted. Also, ASD is noted as providing telephone access for the Pharmacist to assure that both patient and physician are complaint with the registry rules. Stopping rules for the physician and pharmacist (i.e., when a request for drug should be declined), should be described.

The SOP for SEU is needed to expressly define when the patient will be contacted, when the physician will be contacted, or when both will be contacted. It would also be helpful to note which form of communication listed (facsimile, phone or mail) will be used and in which order. The lapse of three days from receiving a survey seems long. (Note, the company states that they will ship the drug with two days for a newly registered pharmacy). There may be certain "red flags" (e.g., a woman noting that she is not using birth control) that could be checked immediately (e.g., within 24 hours) and other "signals" that could be instituted within the three day period. One concern, the SEU review should be viewed as an "Error Prevention Analysis (EPA)" review and not simply as a tracking survey. This EPA mind set should seek to identify and act upon "signals" that there is a possibility of an impending pregnancy and provide immediate feedback to the user, dispenser, and/or prescriber to prevent the pregnancy from occurring.

The initial testing of the ASD system is mentioned but the results are not described. How formally was the test implemented? Did the system work as planned? If not, what changes will be needed? The overview states that the SEU system will be evaluated by several groups, including an independent advisory board. What is the make-up of this board and what responsibilities will it have? Auditing of the initial 100 patients seems like a good idea. Included in the material submitted by SEU to Celgene is a report including the informed consent and survey "forms." If this means that the company will receive actual copies of the informed consent sheet and survey forms, there may be a conflict. The informed consent sheet suggests

consent sheet and survey forms, there may be a conflict. The informed consent sheet suggests that the survey coordinators will be receiving a copy of the form, but it does not mention the manufacturer of the drug. The survey is described as confidential and it states that the information will be kept only by Boston University (BU). This raises the question of whether the SEU informed consent and "survey" has been reviewed by an IRB. If so, are there any confidentiality/privacy concerns with sharing this information with the manufacturer? If the information is to be shared with the manufacturer with any personal identifiers, there needs to be a disclosure to the patient.

39- The statement to physicians, "The brochure entitled *Your Contraceptive Choices*, enclosed in the S.T.E.P.S. folder, should be used as an aid to ensure that patients make choices that they will adhere to", contained in Exhibit M, fails to reinforce to physicians that patients must choose two methods of contraception. Please revise.

40- In addition to the S.T.E.P.S. submission of January 26, 1998, you submitted materials to the Division of Drug Marketing, Advertising and Communications (DDMAC) dated January 8, 1998. These materials include a formulary fact sheet, [ ] J" and the THALOMID™ Access Assistance Program reimbursement brochure. The reference guide would be misleading because it minimizes the importance of the more significant risk information regarding contained in the WARNINGS and PRECAUTIONS section of the labeling by not promoting the risk information in the section labeled "Safety Profile."

We are also enclosing a copy of the label. Please note that the revisions, additions and deletions are noted on the copy. Please revise the adverse events tables to consolidate the presentation of those data into a single table and provide a code for the patients with different diseases in which the events were observed.

Your response should be submitted to NDA 20-785. If you have any questions, please call Mary Jane Walling at 301-827-2268.

Sincerely,

MWeintraub 3/27/98

Michael Weintraub, M.D.
Director, Office of Drug Evaluation V
Center for Drug Evaluation and Research, FDA

REV:JWOODCOCK:03/17/98:03/20/98
REV:WEINTRAUB:03/26/98

a:\janltr2r

cc: NDA 20-785 IR letter
HFD-1/WOODCOCK
HFD-40/ASKINE
HFD-105/WEINTRAUB/WALLING
HFD-530/BIRNKRANT

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-785

MAY 12 1998

Steve Thomas, Ph.D.
Celgene Corporate
7 Powder Horn Drive
Warren, NJ
07059

Dear Dr. Thomas;

We understand that the accrual in the Phillippines of patients in your study E003/P, thalidomide treatment of patients with ENL, is proceeding slowly. We find it desirable to have the full compliment of subjects as discussed during the development of the study design. We recognize that you are putting out your best effort, however you may need to investigate enrolling patients in other parts of the world, for example Brazil or West Africa.

Sincerely yours,

Michael Weintraub

Michael Weintraub, M.D.,
Director Office of
Drug Evaluation V

DEPARTMENT OF HEALTH & HUMAN SERVICES

105 Walling 540

Public Health Service

Food and Drug Administration
Rockville MD 20857

May 26, 1998

NDA: 20-785
Serial Number 052

Steve Thomas, Ph.D.
Celgene Corp.
7 Powder Horn Drive
Warren, NJ 07059
Fax: 732-271-4184

MAY 26 1998

Dear Dr. Thomas:

The revised labeling included with this letter represents the acceptable text for the above mentioned application.

The text is being sent to you in order that you may final the revisions to the S.T.E.P.S.

If you have any questions about this, please call Mary Jane Walling at 301-827-2268.

Sincerely yours,

Michael Weintraub 5/26/98

Michael Weintraub M.D.
Director,
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enc(s): Revised Label

20 Page(s) Withheld

____ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

20 Page(s) Withheld

____ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

9 Page(s) Withheld

____ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

15 Page(s) Withheld

____ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

4 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

Celgene

Dr. Tony de Camp
Room N206, 9201 Corporate Boulevard,
Rockville MD 20850

SEP 3 1997

September 2nd 1997

RE: NDA 20-785

Dear Dr de Camp

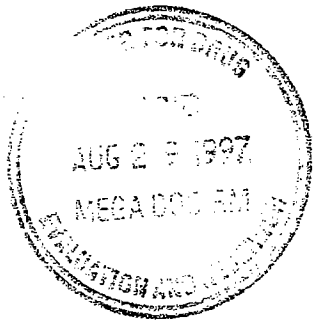
Please find enclosed a copy of Celgene's current SOP for Out of Specification (OOS) results as discussed last Thursday (8/28/97). The section classifying OOS results of replicates is section 5 on page 2. Please call me if you need any additional information.

Best regards

Ali Smith

Alison Smith

29 August 1997



Jonathan Wilkin. M.D.
Director, Division of Dermatological and Dental Drug Products
HFD-540
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Re: NDA 20-785
Thalidomide Capsules
Serial No.: 020
General Correspondence:
Additional Data Collected from LAC USC
CONFIDENTIAL

Dear Dr. Wilkin.

Celgene Corporation acknowledges that it received copies of the data collection forms for the data collected from Los Angeles County Medical Center University of Southern California. In addition. please find enclosed a copy of a recent facsimile requesting these data and minutes from a telephone conference call held between the Division and Celgene 31 July 1997. which is referenced in the facsimile.

Please do not hesitate to call me with any questions or comments.

Sincerely.

Steve Thomas

Steve Thomas. Ph.D.
Vice President. Pharmaceutical Development

29 August 1997

Jonathan Wilkin, M.D.
Director, Division of Dermatological and Dental Drug Products
HFD-540
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Re: NDA 20-785
Thalidomide Capsules
Serial No.: 021
Study E-003/P Updated Listings
CONFIDENTIAL

Dear Dr. Wilkin,

Please find enclosed updated listings for Study E-003/P, a copy of which was hand delivered 28 August to Dr. Kathryn O'Connell. These reflect blinded data from 17 patients, 3 of whom were re-randomized (using a separate randomization). The preparation of an updated interim report is in progress, but will not be available for some weeks.

Celgene plans to submit early next week a draft listing from the 6 patients in Study E-001, to including pharmacokinetic results, and the oral contraceptive drug interaction report (PK-003).

Please do not hesitate to call me with any questions or comments.

Sincerely,

Steve Thomas

Steve Thomas, Ph.D.
Vice President, Pharmaceutical Development

Desk Copies: K.D. White (2 copies)
Mary Jane Walling (letter only)

20-785 N 3

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
Tel 908-271-1001
Fax 908-271-4184

Dr. Tony de Camp
Room N206, 9201 Corporate Boulevard,
Rockville MD 20850

August 27th 1997

Dear Dr de Camp

Per your request, I enclose a hard copy of the documentation that I faxed earlier today, along with copies of our Certificates of Analysis for drug substance batch 574-574-97-001, drug product batches 0091N and 0092N (last 2 validation batches), and drug product batches DEV2117 and DEV2400 (clinical trials batches). Note that the individual values of % Assay for DEV2117 are [ ], and for DEV2400 are [ ]

Please call me if you need any additional information.

Best regards

Alison Smith

Alison Smith

DUPLICATE

NEW CORRESP

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
Tel 908-271-1001
Fax 908-271-4184

26 August 1997

Jonathan Wilkin, M.D.
Director, Division of Dermatological and Dental Drug Products
HFD-540
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Re: NDA 20-785
Thalidomide Capsules
Serial No.: 019
Amendment to a Pending Application:
LOA for Study E-003/P
CONFIDENTIAL

Dear Dr. Wilkin,

Please find enclosed, per Dr. Tony Carreras' request, a letter of authorization (LOA) dated 21 August 1997, from Dr. Tranquilino T. Fajardo, Jr., Leonard Wood Memorial American Leprosy Foundation to Dr. Steve Thomas, Celgene Corporation permitting investigators from the FDA to come to Cebu in September and have full access to all documents and records pertaining to Study E-003/P. Also enclosed please find travel information that was sent to Dr. Carreras.

Please do not hesitate to call me with any questions or comments.

Sincerely,

Steve Thomas

Steve Thomas, Ph.D.
Vice President, Pharmaceutical Development

Celgene

21 August 1997

Jonathan Wilkin, M.D.
Director, Division of Dermatological and Dental Drug Products
HFD-540
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Re: NDA 20-785
Thalidomide Capsules
Serial No.: 018
Amendment to a Pending Application:
LOA for IND 11,359
CONFIDENTIAL

Dear Dr. Wilkin,

Please find enclosed a letter of authorization (LOA) dated 29 June 1993, from Dr. Robert Hastings, Gillis, W. Long Hansen's Disease Center to Dr. Steve Thomas, Celgene Corporation permitting Celgene to reference chemistry, pharmacology, toxicology and previous human experience data from IND 11,359.

Please do not hesitate to call me with any questions or comments.

Sincerely,

Steve Thomas, Ph.D.
Vice President, Pharmaceutical Development

DEPARTMENT OF HEALTH & [illegible]MAN SERVICES — [illegible]blic Health Service

Laboratory Research Branch
GWL Hansen's Disease Center at
Louisiana State University
P.O. Box 25072
Baton Rouge, LA 70894

Tel: 504-346-5785
FAX: 504-346-5786

29 June 1993

Dr. Steve Thomas
Project Manager
Celgene Corporation
7 Powder Horn Drive
P.O. Box 4914
Warren, New Jersey 07059

Dear Dr. Thomas:

We are happy to authorize you to reference our FDA IND #11,359, regarding the chemistry, pharmacology, toxicology, and previous human experience with thalidomide, in Celgene's intended IND submission to the Food and Drug Administration.

Sincerely yours,

Robert C. Hastings, M.D., Ph.D.
Chief, Laboratory Research Branch

ORIGINAL

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
Tel 908-271-1001
Fax 908-271-4194

NC
NEW CORRESP

18 August 1997

Jonathan Wilkin, M.D.
Director, Division of Dermatological and Dental Drug Products
HFD-540
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Re: NDA 20-785
Thalidomide Capsules
Serial No.: 017
Briefing Package #1 for Advisory Committee Hearing
CONFIDENTIAL

Dear Dr. Wilkin,

Please find enclosed 6 copies of the briefing package for the upcoming Advisory Committee Hearing to be held the 4th and 5th of September. Thirty copies have been delivered directly to Tracy Riley. Additional information will be forwarded as soon as it is made available.

Please do not hesitate to contact me with any questions or comments.

Sincerely,

Steve

Steve Thomas, Ph.D.
Vice President, Pharmaceutical Development

Celgene

12 August 1997

Aug 12 1997

Jonathan Wilkin, M.D.
Director, Division of Dermatological and Dental Drug Products
HFD-540
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Re: NDA 20-785
Thalidomide Capsules
Serial No.: 016
Amendment to Pending Application
Response to FDA Request for
Additional Information
CONFIDENTIAL

Dear Dr. Wilkin,

A request for additional information for Studies PK-001, PK-004 and PK-005, all of which were conducted at [redacted] was made by representatives of the Division of Dermatological and Dental Drug Products to representatives of Celgene Corporation during a 31 July 1997 teleconference. [redacted] has provided these documents and they are enclosed as described below.

The requested documents for Study PK-001 are in Attachment 1. The documents include the IRB-approved informed consent document; a random selection of 50% of the available case report forms (CRFs) including the computer generated output for selecting the CRFs, the laboratory reference ranges for the clinical laboratory studies specific to the PK-001 protocol, and a complete list of laboratory tests available at [redacted] (the analytical laboratories used for this study).

Documents for Studies PK-004 and PK-005 are in Attachments 2 and 3, respectively. Each set of documents includes IRB-approved informed consent documents, a random selection of 50% of the available CRFs including the computer generated output for selecting the CRFs, the laboratory reference ranges specific to the clinical laboratory studies conducted under Protocols PK-004 and PK-005 at [ ] and a complete list of laboratory tests available at [ ].

Please do not hesitate to contact me with any questions or comments.

Sincerely,

Steve CLA

Steve Thomas, Ph.D.
Vice President, Pharmaceutical Development

BM--

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
Tel 908-271-1001
Fax 908-271-4184

ORIGINAL

1 August 1997

Jonathan Wilkin, M.D.
Director, Division of Dermatological and Dental Drug Products
HFD-540
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Re: NDA 20-785
CONFIDENTIAL
Thalidomide Capsules
Serial No. 015
Amendment to Pending Application:
Draft Patient Brochure

Dear Dr. Wilkin:

Enclosed please find a DRAFT of the information packet to be distributed to patient as part of Celgene Corporation's System for Thalidomide Education and Prescribing Safety (STEPS) program. Celgene plans to implement the STEPS program with the commercialization of thalidomide. The objective of this program is to prevent fetal exposure to thalidomide by fully informing patients of the consequences of such exposure. This comprehensive program will be directed to all patients who are candidates for thalidomide therapy, both male and female, and to their health care providers. In addition, distribution controls will be put in place to ensure compliance with the program as will a mandatory surveillance program to monitor program compliance and outcome.

The enclosed packet includes an information brochure describing the STEPS program and program monitoring, the patient brochure, the informed consent document and the proposed package configuration. We are submitting a total of 14 copies for your review.

Please contact me with any questions or comments on the enclosed brochures.

Sincerely,

Steve CA

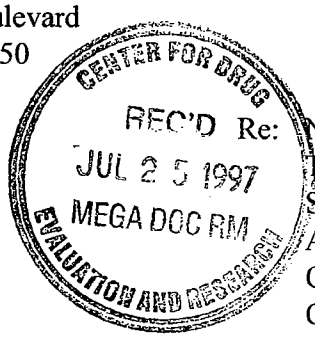
Steve Thomas, Ph.D.
Vice President Pharmaceutical Development

BM
ORIGINAL

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
Tel 908-271-1001
Fax 908-271-4184

25 July 1997

Jonathan Wilkin, M.D.
Director, Division of Dermatological and Dental Drug Products
HFD-540
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850



Re: NDA 20-785
Thalidomide Capsules
Serial No.: 014
Amendment to a Pending Application:
Clinical Data
CONFIDENTIAL

Dear Dr. Wilkin,

Celgene Corporation recently received four diskettes containing clinical data representing patients treated under IND 11,359 held by the U.S. Public Health Service (USPHS). These data have been provided to Celgene for incorporation into NDA 20-785. Copies of these diskettes were recently hand delivered to Kevin Darryl White (cover letters enclosed). Enclosed in this submission are copies of the data collection sheets (Appendix 1) and the data listings obtained from these diskettes (Appendix 2). Celgene is in the process of analyzing these data and has encountered several issues requiring clarification. For the present, only minimal analyses are possible.

To enable Celgene to undertake a thorough and rigorous analysis of these data, we would welcome your assistance in clarifying the discrepancies and omissions in the analysis of these files that are listed below.

As an alternative, or possibly in addition to your efforts, Celgene would appreciate hard copies of the individual CRFs used in the generation of the diskettes so that it can undertake an audit of the hard copy *versus* the electronic version. In this way, we may be able to verify and clarify the omissions and discrepancies.

Please let me know if hard copies of the CRFs are available for Celgene to review.

The discrepancies and omissions noted while reviewing these files listed below.

1. The file titled 110.xls has its Patient ID listed as 120. There is another file titled 120.xls that also has a Patient ID listed as 120. We will assume the correct ID to be 110, until this issue is clarified. Also the file titled 231.xls has its Patient ID listed as 213. We will assume the correct ID to be 231, until this issue is clarified.

2. The following files do not have a number listed in the patient ID column on Sheet 1:

108.xls	pat 138.xls	pat186.xls	227.xls
129.xls	pat 139.xls	pat 187.xls	228.xls
pat 133.xls	153.xls	pat 188.xls	229.xls
pat 134.xls	173.xls	pat 189.xls	230.xls
pat 135.xls	174.xls	pat 199.xls	

   Until this issue is resolved, we will assume the file name to correctly reflect the patient ID.

3. Demographic and adverse event data are missing. These data are on Sheets 2 and 3. All patients on all four diskettes have Patient ID 133 and identical data on Sheets 2 through 3.

4. If demographic data will be provided in the future, please include the following:

   a. Race codes
   b. Meaning of "virtual code"

5. The contents of the file for Patient 227 is completely blank.

6. For many variables, a yes / no response is possible, with responses for "yes" entered as "1". In many cases, however, the response is blank. For purposes of analysis, we will assume all blanks to be "no"; the listings will nonetheless show blanks for these responses.

7. With respect to the medication data, the variable "change code" lists codes for responses "1" through "5". Many observations have responses "6", "7", and "8" or composite responses such as "6 (8)" and "1, (8)". Until resolved, these will be treated as "missing."

8. We have the following questions on the Physical Examination data:

   a. What is the code for "5" on the cutaneous Physical Exam? Until resolved, we will assume this to represent missing or illegible responses.

   b. On the non-cutaneous Physical Exam there are inconsistent column headers in the electronic datasets. Some patients have two columns headed "nephritis", and some patients have no column headed "arthritis". Please note that the duplication of "nephritis" also appears on the paper data collection form.

   c. With respect to the non-cutaneous Physical Exam, are there codes for "other" observations?

Please do not hesitate to call me with any questions or comments.

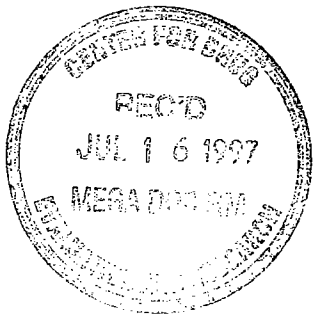
Sincerely,

Steve Thomas, Ph.D.
Vice President, Pharmaceutical Development

Desk copy: Mary Jane Walling

DUPLICATE

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
Tel 908-271-1001
Fax 908-271-4184



16 July 1997

Jonathan Wilkin, M.D.
Director, Division of Dermatological and Dental Drug Products
HFD-540
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Re: NDA 20-785
Thalidomide Capsules
Serial No.: 013
PK Study Commitment

Dear Dr. Wilkin,

On 1 July 1997 a telephone conference call was held between representatives of the Division and Celgene Corporation. In accordance with discussions during this call, Celgene Corporation is stating herein that it is committed to conducting a study of the bioavailability of the proposed commercial formulation of thalidomide 50 mg capsules [redacted] A draft protocol and minutes of the telephone conference call have been submitted to IND 48,177 (16 July; Serial No. 048), with numerous desk copies. Celgene is committed to conducting this study once safety and stability issues associated with the reference material are resolved.

It is also our understanding from the telephone conference call that the outstanding Division of Biopharmaceutics issues pertaining to NDA 20-785 will be resolved with the submission of the final protocol described above and the draft report for Study PK-003 (which describes the pharmacokinetics in females, multiple dose pharmacokinetics, and drug interaction with oral contraceptives), Study PK-006 (a comparison of single dose pharmacokinetics in the fed and fasted states); and Study E-001 (which describes steady state levels in ENL patients). If the Agency's view is not in accord with this understanding, please contact the undersigned at your earliest convenience.

Please do not hesitate to call me with any questions or comments.

Sincerely,

Steve

Steve Thomas, Ph.D.
Vice President, Pharmaceutical Development

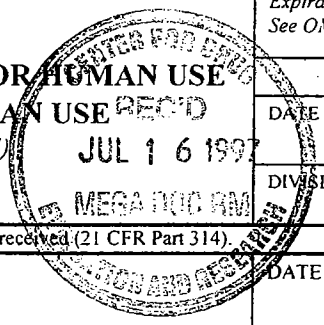
002590

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001.
Expiration Date: April 30, 1994.
See OMB Statement on Page 3.



FOR FDA USE ONLY	
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS

NOTE: No application may be filed unless a completed application for has been received (21 CFR Part 314).

NAME OF APPLICANT	DATE OF SUBMISSION
Celgene Corporation	16 July 1997
APPLICANT ADDRESS *(Number, Street, City, State, Country, and ZIP Code or Mail Code)*:	TELEPHONE NO. (Include Area Code)
7 Powder Horn Drive Warren, NJ 07059	(908) 271-1001
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued) 20-785

DRUG PRODUCT

ESTABLISHED NAME *(e.g., Proper name, USP/USAN)*	PROPRIETARY NAME *(if any)*	
Thalidomide	Synovir™	
CODE NAME (if any)	CHEMICAL NAME	
	alpha-(Nphthalimido)glutarimid	
DOSAGE FORM:	ROUTE OF ADMINISTRATION:	STRENGTH(S)
Capsule	Oral	50 mg

PROPOSED INDICATIONS FOR USE:

Acute treatment of erythema nodosum leprosum (ENL) as well as for the maintenance therapy for prevention and suppression of ENL occurrence.

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CRF Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), AND DRUG MASTER FILES (21 CFR 314.420) REFERRED TO IN THIS APPLICATION:

IND	Serial No(s)	Protocol	IND	Serial No(s)	Protocol
48,177	008, 011	E-001	[ ]	000	W-001
	031	E-003		029	W-002
	029	PK-004		045	PK-001
	035	PK-005		046	PKUK-001
				088	PK-003
INDs held by Celgene Corporation				046	THAL-3

INFORMATION ON APPLICATION

TYPE OF APPLICATION (Check one)

☐ THIS SUBMISSION IS A FULL APPLICATION (21 CFR 314.50) ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN NDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

TYPE SUBMISSION (Check one)

☐ PRESUBMISSION ☐ AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION

☐ ORIGINAL APPLICATION ☐ RESUBMISSION ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION (e.g., Part 314.70(b)(2)(iv)) _____

PROPOSED MARKETING STATUS (Check one)

☐ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (Rx) ☐ APPLICATION FOR AN OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC

FORM FDA 356h (5 96)

002587

CONTENTS OF APPLICATIONS	
This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Summary (21 CFR 314. 50 (c))
	3. Chemistry, manufacturing, and control section (21 CRF 314.50 (d) (1))
	4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)
	b. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i))
	c. Labeling (21 CFR 314.50 (e) (2) (ii))
	i. draft labeling (4copies)
	ii. final printed labeling (12 copies)
	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))
	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))
	7. Microbiology section (21 CFR 314.50 (d) (4))
	8. Clinical data section (21 CFR 314.50 (d) (5))
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))
	10. Statistical section (21 CFR 314.50 (d) (6))
	11. Case report tabulations (21 CFR 314.50 (f) (1))
	12. Case report forms (21 CFR 314.40 (f) (1))
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. OTHER (Specify)

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR Part 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71 and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
Steve Thomas, Ph.D.	Steve Thomas	16 July 1997

ADDRESS (Street, City, State, Zip Code)	TELEPHONE NO. (Include Area Code)
7 Powder Horn Drive Warren, NJ 07059	(908) 805-3914

WARNING: a WILLFULLY FALSE STATEMENT IS A CRIMINAL OFFENSE. U.s.c. Title 18, Sec. 1001.)

FORM FDA 356h (5/96)

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Reports Clearance Officer, PHS
Hubert H. Humphrey Building, Room 721-B
200 Independence Avenue, S.W.
Washington, DC 20201
Attn: FDA

and to: Office of Management and Budget
Paperwork Reduction Project (0910-0001)
Washington, DC 20503

Please DO NOT RETURN this application to either of these addresses.

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
Tel 908-271-1001
Fax 908-271-4184

16 July 1997

Kevin Darryl White
Project Manager
Division of Dermatological and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Re: NDA 20-785
Thalidomide Capsules
Clinical Data
CONFIDENTIAL

Dear Mr. White:

Attached please find enclosed a fourth diskette containing new clinical data on an additional 10 ENL patients treated with thalidomide under IND 11,359. This information will allow further assessment of time to response and concomitant medication use in support of the pending application, NDA 20-785. A hard copy of these data will follow shortly.

Please do not hesitate to contact me with any questions or comments.

Sincerely,

Steve Thomas, Ph.D.
Vice President, Pharmaceutical Development

cc: Jonathan Wilkin, M.D., HFD-540 / cover letter only
Mary Jane Walling, HFD-550 / cover letter only

ORIGINAL

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
Tel 908-271-1001
Fax 908-271-4184

ORIG AMENDMENT

17 June 1997

Jonathan Wilkin, M.D.
Director, Division of Dermatological and Dental Drug Products
HFD-540
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Re: NDA 20-785
Thalidomide Capsules
Serial No.: 012
Response to Questions
Facsimile of 9 May 1997
CONFIDENTIAL

Dear Dr. Wilkin,

Please refer to your facsimile dated 9 May 1997 requesting additional information for Study L-001, entitled "Thalidomide in the Treatment of Erythema Nodosum Leprosum: A placebo Controlled Study", a study included in NDA 20-785. Responses to your questions are provided following this cover letter. For your convenience, each question is stated verbatim, followed by Celgene Corporation's response. A copy of the Division's facsimile is also enclosed in Attachment 1.

Photocopies from the source medical records have been provided in support of responses. We have endeavored to provide the best possible copies, however, given the age of the records, many are difficult to read. Please do not hesitate to call if additional copies are needed or in the event of additional questions or comments.

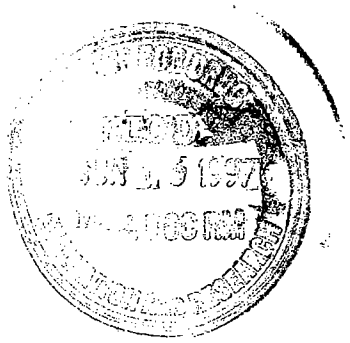
Sincerely,

Steve Thomas, Ph.D.
Vice President, Pharmaceutical Development

Desk copies: Brenda Vaughan, M.D.; Kevin Darryl White; and Jonathan Wilkin, M.D.

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
Tel 908-271-1001
Fax 908-271-4184

16 June 1997



Kevin Darryl White
Project Manager
Division of Dermatological and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Re: NDA 20-785
Thalidomide Capsules
Clinical Data
CONFIDENTIAL

Dear Mr. White:

Attached please find enclosed three diskettes containing new clinical data on 97 ENL patients treated with thalidomide under IND 11,359. This information will allow further assessment of time to response and concomitant medication use in support of the pending application, NDA 20-785. A hard copy of these data will follow shortly.

Please do not hesitate to contact me with any questions or comments.

Sincerely,

Steve Thomas, Ph.D.
Vice President, Pharmaceutical Development

cc: Jonathan Wilkin, M.D., HFD-540 / cover letter only
Mary Jane Walling, HFD-550 / cover letter only

ORIGINAL

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
Tel 908-271-1001
Fax 908-271-4184

ORIG AMENDMEN

BC

12 June 1997

Jonathan Wilkin, M.D.
Director, Division of Dermatological and Dental Drug Products
HFD-540
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Re: NDA 20-785
Thalidomide Capsules
Serial No.: 011
Amendment to Pending Application
Chemistry, Manufacturing and Controls
CONFIDENTIAL

Dear Dr. Wilkin,

In accordance with 21 CFR Celgene Corporation herewith submits an amendment to NDA 20-785, Synovir® (thalidomide) Capsules, containing information pertaining to Chemistry, Manufacturing and Controls.

Please refer to the CMC presubmission that was submitted on October 24, 1996 and amended on February 25, 1997 and April 1, 1997. Please also refer to the FDA483 issued to Celgene on February 28, 1997 after the pre-approval inspection of the Warren, New Jersey facility. In the FDA483 Celgene was cited for using [ ] in the manufacture of the drug substance which was not submitted to the NDA. This procedure is [ ] the final product. We are herewith submitting, for your review, the full [ ] procedure with the [ ] Minor changes have been made to the procedure since the submission of the NDA CMC section, and they are also described herein.

This amendment contains two additional updates, a revised SOP for the dissolution method and a stability update. The revised SOP for the dissolution contains instructions for performing single point withdrawals in addition to the profiles. The updated statistical analyses for the [ ] stability data of the NDA batches now support [ ] shelf life in HDPE bottles.

A summary of the enclosed items is found on page 000978 of this submission. If you have any questions or comments regarding this amendment, please contact me at (908) 271-4137.

Sincerely,

Norma P. Loeffler

Norma P. Loeffler
Associate Director, Regulatory Affairs

Enclosures in duplicate: 2 volumes, 2 diskettes
cc: Dr. Wilson DeCamp, Chemistry Team Leader (cover letter only)
New Brunswick Resident Post (Ms. Regina Brown, Pre Approval Program Manager) (2 volumes only)
New Jersey District Parsippany Office (Mr. Ray Abrahams, Compliance Branch Director) (2 volumes only)
New Jersey District Parsippany Office (Mr. Matthew Spataro, Investigator) (cover letter only)

ORIGINAL

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
Tel 908-271-1001
Fax 908-271-4184

2 June 1997

BB

NDA ORIG AMENDMENT

Jonathan Wilkin, M.D.
Director, Division of Dermatological and Dental Drug Products
HFD-540
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Re: NDA 20-785
Thalidomide Capsules
Final Study Reports:
90-Day Mouse Study
PK-005 (Biopharmaceutics)
Serial No.: 009
CONFIDENTIAL

Dear Dr. Wilkin,

Please refer to NDA 20-785, originally submitted 20 December 1996. Enclosed are two final study reports: the final 90-Day Mouse Study Report and the final report for the metabolism study conducted in patients with Hansen's disease (PK-005). The latter report had been included in draft in the original NDA submission.

Please do not hesitate to call with any questions or comments.

Sincerely,

Steve CA

Steve Thomas, Ph.D.
Vice President, Pharmaceutical Development

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

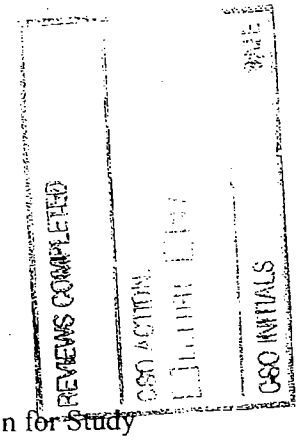
CSO INITIALS DATE

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
Tel 908-271-1001
Fax 908-271-4184

23 May 1997

BM
NDA ORIG AMENDMENT

Jonathan Wilkin, M.D.
Director, Division of Dermatological and Dental Drug Products
HFD-540
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850



Re: NDA 20-785
Thalidomide Capsules
Serial No.: 008
Response to Questions
Facsimile of 9 May 1997
CONFIDENTIAL

Dear Dr. Wilkin,

Please refer to your facsimile dated 9 May 1997 requesting additional information for Study L-001, entitled "Thalidomide in the Treatment of Erythema Nodosum Leprosum: A placebo Controlled Study", a study included in NDA 20-785. These questions were first communicated 5 May 1997 in a telephone conference call initiated by representatives of the Division of Dermatological and Dental Drug Products (Dr. Vaughan, Mr. Kevin Darryl White, and you). In preparation of the study report, the medical records at the Gillis W. Long Hansen's Disease Center (GWLHDC), were reviewed and data were transcribed onto Case Report Forms (CRFs). Photocopies of source documents were not taken systematically. Therefore, in order to respond completely to all questions, Celgene Corporation (Celgene) will need to access the source medical records.

Below are responses to those questions that can be addressed now. For your convenience, the question is stated verbatim, followed by Celgene's response. A copy of the Division's facsimile is enclosed in Attachment 1.

1. **According to the L-001 Study Report, twenty-seven patients were identified as entering the double-blind study between June 12, 1967 and February 10, 1969. This group of patients was considered the original study sample. Two patients discontinued prior to receiving double-blind treatment.**

Twelve patients were identified as having received thalidomide during the double-blind treatment period, and 12 patients were identified as receiving placebo, with one patient (No. 2808) participating in two double blind placebo treatment courses. One patient, No. 2855, appears not to be assigned.

However, the original published study conducted by Dr. Hastings identifies 23 trials as double blinded, with 15 double blind trials being conducted with thalidomide and only 8 trials conducted with placebo. There were a total of 44 single and double blind trials conducted in 22 patients.

Please reconcile these different patient numbers.

Celgene acknowledges that there is a discrepancy between the number of patients identified by the retrospective review of medical records and the publication of Dr. Hastings in Clinical Pharmacology and Therapeutics Vol 11 pages 481-487, (1970). The Celgene database is more comprehensive, having identified 5 more patients randomized to treatment than were included in the publication. One of the patients, Patient 2553 never received drug. The publication does not provide sufficient detail to allow a matching of patients and there is no other written record available to Celgene to identify the 4 remaining patients who had been excluded from the publication. Nonetheless, the results based on the complete database in the study report and the subset in the publications are consistent in demonstrating a significant reduction in erythema nodosum leprosum (ENL) based on temperature and lesion assessment. in the patients treated with thalidomide.

2. **Provide documentation of the index date for the following patients: Patient # 1707, 2033, and 2078. The index date is defined as the first date the double-blind treatment when** [sic] **"Bottle A" was received.**

The index date for each patient was listed in Appendix 5 of Study L-001, page 08 0133 of NDA 20-785. The supporting source documents (Physician's Orders) are provided in Attachment 2 for Patients 1707 and 2078. The source documents for Patient 2033 will be provided as soon as they are obtained from the archives at Carville.

We have scheduled a company representative to collect the copies of the requested progress notes and doctors orders from GWLHDC during the week of 26 May. We will submit these documents as soon as they are available. In the meanwhile, please feel free to call with any questions or comments regarding these responses.

Sincerely,

Steve Thomas -KSK

Steve Thomas, Ph.D.
Vice President, Pharmaceutical Development

Date: 5/09/97

To: Steve Thomas, Ph.D.

From: Jonathan Wilkin, M.D.

Subject: NDA 20-785 Summary Comments

As per our teleconference on May 5, 1997, we have the following questions regarding Study L-001.

1. According to the L-001 Study Report, twenty-seven patients were identified as entering the double-blind study between June 12, 1967 and February 10, 1969. This group of patients was considered the original study sample. Two patients discontinued prior to receiving double-blind treatment.

   Twelve patients were identified as having received thalidomide during the double-blind treatment period, and 12 patients were identified as receiving placebo, with one patient (No. 2808) participating in two double blind placebo treatment courses. One patient, No. 2855, appears not to be assigned.

   However, the original published study conducted by Dr. Hastings identifies 23 trials as double blinded, with 15 double blind trials being conducted with thalidomide and only 9 trials conducted with placebo. There were a total of 44 single and double blind trials conducted in 22 patients.

   Please reconcile these different patient numbers.

2. Provide documentation of the index date for the following patients: Patient# 1707, 2033, and 2078. The index date is defined as the first date the double-blind treatment when "Bottle A" was received.

3. Please verify that the Agency has received the complete progress notes for the following patients: Patient# 2078, 1707, 2603, 2793, 869, and 2703.

   In addition, provide the physician's orders for Patients No.# 869, 1274, 2033, 2603, 2643, 2655, 2752, 2808, 2804, 2840, 2855, and 2892.

4. Please clarify the purpose of Appendix 3 "Listing of Patients at the National Hansen's Disease Center in Carrville, Louisiana." The following are examples of the inconsistencies noted between the listings for Appendix 3 and other documentation provided in support of Study L-001:

Patient No. 2703	The Index Date of 01/29/68 was provided. Patient received double blind treatment from Bottle A, identified as a placebo (failure), verification provided in Appendix 16 as "Dr.'s progress note 2/5/68: Code broken today - Bottle "A" contained placebo: "B" contained thalidomide". However, no entry was provided for 2/5/68. the patient was switched to Bottle "B" on the AM of 2/2/68. However, the patient listing from appendix 3 provided the following information: 1/29/68 - 3/7/69; Placebo: 3/12/69 - 10/1/69. Was this patient on Thalidomide or Placebo?
Patient No. 2643	Index Date (01/15/68), received double blind treatment from Bottle "A", identified as placebo (success) via documentation from progress noted dated 01/22/68. However, the patient listing gives date of 1/15/67 - 9/3/68, for receiving thalidomide.
Patient No. 2553	This patient was identified as a 65-y/o Asian male, who died of acute myocardial infarction on [ ] the day treatment was to have commenced. A review of the medical chart showed no evidence that he received any doses of "Bottle A". However, the patient listing gives a date of [ ] (rec'd 4 doses).

5. Please identify and provide the dates of the single blind study periods for patients submitted for Study L-001.

6. Please explain the reference to "blue pills" which is noted in Patient No. 1274 ENL Assessment dated 7/7/68 ("Will begin on 'blue pills' in AM.")

7. Please provide evidence of double blinding for the following patients:

   1274, 1707, 2033, 2603, 2757, 2840, 2855, 2323, 2773, and 2892.

8. Please provide verification for the contents of Bottle "A" for patient #2703.

9. Were the ENL Assessments that were "verbatim from Progress Notes," as provided in Appendix II, edited for references only to ENL skin lesions, fever, contents, or assignments to Bottles A or B; or, were all progress notes generated during the study period actually transcribed?

10. Please provide for each patient, all progress notes generated during the pre-treatment (Days -4 to -1), double blind treatment (Days 1-4 or 5), and crossover or continued treatment periods which followed.

If you have any questions, please call Mr. Kevin Darryl White at (301) 827-2020. Thank you.

CLINICAL RECORD — **DOCTOR'S ORDERS** [redacted]

DATE AND TIME | Rx | DRUG ORDERS

3/?/68 — (1) Continue Bottle "A" (present medication) Caps ÷ QID × 4 more days
[signature]

3/8/68 — (1) Doxezide caps ii daily [illegible] × 4 days.
(2) Mylanta 3 ii + Gelusil Tab ii q4h. while awake
[signature]

3/8/68 — (1) Urine culture, sensitivity and colony count today
(2) Declomycin 150 mgm QID x 10 days
[signature]

3/11/68 — (1) Continue [illegible] 100 mgm QID, [illegible] x 7 days
Then ask for new order [signature]
(2) DC [illegible] + Seconal
(3) Darvon 65 — ii Q4h PRN pain
(4) Chloral hydrate for [illegible] h.s. [illegible]
[signature]

(Continued on reverse side)

PATIENT'S IDENTIFICATION (For typed or written entries give: Name—last, first, middle; grade; date; hospital or medical facility)

REGISTER NO. [ ] | WARD NO. [ ]

DOCTOR'S ORDERS
Standard Form 508
508-107

000447

CLINICAL RECORD

DATE AND TIME START	DATE AND TIME STOP	Rx	DRUG ORDERS (Another brand of a generically equivalent product, identical in dose, age form and content of active ingredient(s), may be administered UNLESS checked here)	DOCTOR'S SIGNATURE	
			Remain in		
		1	~~Admit to infirmary Thursday afternoon (3/1)~~		
		2	~~Dx: Thalidomide trial~~		
		3	~~N. P. O. after midnight Thursday~~		
		4	~~Friday morning (3/1):~~		
			~~a) D.C. all anti-reaction treatment including cortico-steroids~~		
			b) ~~No ASA or other anti-pyretic~~		
			c) ~~Continue current anti-leprosy treatment~~		
			d) ~~Demerol 50-100 mgm. I.M. q 3-4 h. PRN pain x 10 days~~		
			e) ~~Codiene gr. i P.O. q.3-4 h. PRN pain x 10 days~~		
			f) ~~Seconal gr. iss-iii P.O. h.s. PRN x 10 days~~		
		5	BP, P, and Temp. q.i.d. and record		
		6	The following lab studies to be done: Friday (3/1), Monday (3/4), Wednesday (3/6), Friday (3/8), and Monday (3/11)		
			a) HCT, Hgb, WBC & diff., reticulocyte count		
			b) Urinalysis, including urine urobilinogen		
			c) Stool for occult blood		
			d) Coomb's test		
			e) Total and direct bilirubin, alkaline phosphatase, SGOT, cholesterol		
		7	Beginning Monday A.M. (3/4) Bottle # A caps i q.i.d. P.O. x 4 days, then ask for new orders		
		8	Please have patient sign two release forms for the use of Thalidomide for the treatment of ENL (one for me, and one for the patient's chart).		
			Thank you		

(Continued on reverse side)

PATIENT'S IDENTIFICATION (For typed or written entries give Name—last, first, middle; grades; name hospital or medical facility)

REGISTER NO. [ ]

WARD NO. [ ]

DOCTOR'S ORDERS
Standard Form 508
508-107

CLINICAL RECORD

DOCTOR'S ORDERS
(Sign all orders)

DATE AND TIME START	DATE AND TIME STOP	Rx	DRUG ORDERS (Another brand of a generically equivalent product, identical in dosage form and content of active ingredient(s), may be administered UNLESS checked here)	DOCTOR'S SIGNATURE	NURSE'S SIGNATURE
6/6		1.	Admit to infirmary Thursday afternoon (6/8)		
		2.	Diagnosis: Thalidomide trial		
		3.	N. P. O. after midnight Thursday		
		4.	Friday morning (6/7):		
			a) D.C. all anti-reaction treatment, including corticosteroids		
			b) No ASA or other anti-pyretic		
			c) Continue current anti-leprosy treatment		
			d) Demerol 50- 100 mgm. I.M. q. 3-4 h. PRN pain X 10 days		
			e) Codiene gr. ½ P.O. q. 3-4 h. PRN pain X 10 days		
			f) Seconal gr. iss- iii P.O. h.s. PRN sleep X 10 days		
		5.	BP, P, and Temp. q.i.d. and record		
		6.	Weigh patient daily and record		
		7.	The following lab studies to be done: Friday (6/7), Monday (6/10), Wednesday (6/12), Friday (6/14), and Monday (6/17).		
			a) Hematocrit, Hemoglobin, direct platelet count		
			b) clotting time, clot retraction time, quantitation of clot retraction (by amount of serum expressed), and presence or absence of fibrinolysis		
			c) Qualitative cryoproteins		
			d) Stool for occult blood		
			e) Cholesterol and quantitative urine urobilinogen (2 hour afternoon sample)		
			f) Prothrombin time		
			g) Partial thromboplastic time, Quantitation Fibrinogen		
		8.	Beginning Monday A.M. (6/10) Bottle # A caps 1 q.i.d. P.O. X 4 days, then ask for new orders		
		9.	Please have patient sign two release forms for the use of Thalidomide for the treatment of ENL (one for me, and one for the patient's chart).		
			Thank you		

(Continued on reverse side)

PATIENT'S IDENTIFICATION (For typed or written entries give: Name—last, first, middle; also date; hospital or medical facility)

REGISTER NO. [redacted]

WARD NO. [redacted]

DOCTOR'S ORDERS
Standard Form 508
508-107

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Steven Thomas, Ph.D.
Vice President
Celgene Corporation
7 Powder Horn Drive
Warren, NJ 07059

APR 10 1997

Dear Dr. Thomas:

As per our teleconference on February 11, 1997, we have the following comments regarding the above-mentioned application.

1. In your NDA submission you stated that "thalidomide in the treatment of ENL has been designated for review under 21 CFR Subpart E." We would like to clarify several points:

   a. Subpart E status was never formally granted, because the information required to evaluate this was not received until the NDA submission.
   b. Subpart E is predominantly an IND-related rule whose provisions are intended to expedite development of an important subset of drugs.
   c. A major benefit conferred on the sponsor under Subpart E is the ability to obtain multiple and timely meetings with the FDA throughout drug development. Even though Subpart E was never formally granted, Celgene has been provided such opportunity.
   d. Subpart E confers little benefit once the NDA is submitted.

2. The more important the endpoint, the "earlier" in drug development approval can occur. Drugs that successfully treat life-threatening or severely debilitating disease may well need phase 4 studies, because of the limited amount of data that may be sufficient to support approval when there is a major benefit demonstrated. Occasionally, we have referred to such major endpoints as "Subpart E-type endpoints", as a shorthand mode of expressing "the treatment of life-threatening or severely debilitating disease", even though Subpart E is really not the issue. In the future, we will endeavor to avoid this jargon, and, instead, state "the treatment of severely debilitating disease" with "debilitating disease" meaning "disease or conditions that cause major irreversible morbidity."

3. The choice of clinical endpoints and labeled indication must ultimately be driven by the data. Choosing an endpoint in study protocols that would demonstrate a major benefit, eg,

the treatment of the neuritis of the ENL syndrome, will involve the judicious selection of accompanying safety measures. Further, studies in the US and in the Philippines require the same standard of care, including monitoring for neuropathy and management of neuritis and other components of the complicated ENL syndrome. Although Sheskin has asserted a positive effect of thalidomide on neuritis, key elements in your NDA submission are not supportive:

a. L-001 did not exclude, but also did not assess neuropathy.
b. L-002 was based on a protocol that would give prednisone for "significant" neuritis.
c. Iyer, et al, found no difference between thalidomide and aspirin in the treatment response of neuritis.

Thus, if you wish to choose neuritis as an endpoint for thalidomide monotherapy, a more intensive safety and monitoring program will be needed.

4. You have already been alerted to the Agency's plan to send personnel to harvest the primary study data that exist at Carville, Los Angeles and Martinez. This unusual effort by the Agency underscores both (1) the Agency's recognition of the important potential benefits to public health consequent on the development of thalidomide AND (2) the inadequacy of the information in your current NDA submission. Given this status, if the Agency's data harvest at Carville, Los Angeles and Martinez falls short of adequate evidence, then your ongoing studies, eg, E-003/P, may become phase studies. Since data from ongoing studies might be pivotal to an eventual approval, we offer close consultative support to you in the modification of these various protocols.

5. In addition to the efficacy data, we will be looking for dose-ranging information in the current submission, in what we harvest, and in progress reports of ongoing studies.

6. Although in our earlier discussions we all considered thalidomide to be insoluble in common media, new information has emerged. We now know of a safe solvent for oral usage. You will need to demonstrate comparative bioavailability between your product and the solution reference. Such a study could be done in a number of ways:

a. You could re-do the comparative bioavailability study between your product and the Tortuga product, adding

the solution reference.

b. You could add a solution treatment to the already planned food/fasting study.

c. You could initiate an entirely new study comparing the solution to your to-be-marketed product.

7. While you submitted for our review a copy of a journal article detailing the stereospecific disposition of thalidomide in man, we would like Celgene to commit to determining the stereospecific disposition of thalidomide in man in phase 4. Initially, this could be done by taking peak/trough samples in an ongoing clinical trial of thalidomide and analyzing them via a stereospecific technique. The need for additional data would be based on the outcome of this study.

8. We also remind you that we have yet to receive the results of the fecal sample analysis from the ongoing study. Since the urinary excretion of thalidomide is extremely low, this information is critical to understanding the fate of thalidomide in man. In process

9. Thalidomide products used in the previous dose-ranging studies and efficacy studies should be characterized.

10. Please convey to us your usage of the term "ENL." As you know, in the literature it refers to both the entire syndrome and the skin lesions only. Please let us know how you will be referring to (1) the entire syndrome and (2) the skin lesions.

11. Depending on what is discovered in our efforts to harvest primary study data, such additional information may be regarded as a major amendment which would extend the review clock.

12. We recommended the following changes in your protocols:

a. E-003/P

(1) Protocol E-003/P should be revised to adequately protect patients with potentially debilitating symptoms of ENL, enrolled in this study. Patients with ENL neuritis should <u>not</u> be enrolled. Development of acute ENL neuritis, numbness or

paresthesia during the study should be considered a treatment failure, and the patient should be terminated from the study and treated appropriately.

(2) *The original inclusion specifically of neuritis in Protocols E-003/P and E-003 (proposed) was presented to the Division based on summaries alleging adequate responses to monotherapy. Subsequently, as noted under L-002, monotherapy is prohibited by protocol in the presence of significant neuritis. If Protocol L-002 has been amended to include thalidomide alone for neuritis, please provide a complete current protocol.*

(3) *Patients who present with evidence of a new eruption, possibly a drug eruption, should be discontinued from the study and considered an adverse event. In addition, the relationship to thalidomide should be evaluated. A biopsy may be indicated.*

(4) *Patients with persistent or increasing peripheral edema should be assessed and the relationship to thalidomide therapy, ENL disease progression, or other metabolic causes should be established. The appropriate treatment and/or criteria for discontinuation from the study for persistent or increasing peripheral edema should be stated in the protocol.*

Additional Protocol Comments:

(5) *A negative serum pregnancy test should be obtained prior to study entry. Monthly, or more frequent, pregnancy testing should be instituted during the study when the contraceptive method is bilateral tubal ligation. An additional contraceptive method should be required, since bilateral tubal ligation also has a failure rate.*

(6) *The use of clofazimine within one month should be an exclusion criterion.*

(7) *Acetaminophen (Panacetamol) may be used as an*

antipyretic during the first 72 hours of the study, and after the recording of the oral temperature.

The use of anti-inflammatory agents, including non-steroidals, which might be beneficial in the treatment of ENL should not be permitted during the study. A "washout " period prior to study entry which reflects the pharmacology of anti-inflammatory agents should be established.

(8) Ordinal quantification is needed to analyze the global assessments categorized as mild, moderate or severe for systemic symptoms of chills, malaise, anorexia, arthralgias, orchitis, and others. Degree ranges for fever severity should be provided.

(9) Mild, moderate, and severe categories should be established for grading neuritis and other neurological symptoms. A patient "visual analog scale" could be useful.

(10) In the August 12, 1996, version on page 9, the first sentence under "Lack of Response" is ambiguous. The statement should definitively discriminate between criteria of failure and discontinuation. As currently written, these judgments appear to be uncharacterized and could be arbitrary.

(11) Patients should not be re-enrolled in this study.

(12) A maintenance and suppressive therapy protocol should be developed with clearly defined end points, if the sponsor intends to continue to treat ENL patients in the Philippines under IND 48,177.

(13) Electrophysiological monitoring, vibratory, and/or monitoring ankle jerks in addition to patient queries should be added for safety monitoring in order to assess the risk of thalidomide induced neuropathy for chronic use studies in the United States and the in Philippines.

(14) Females of childbearing potential with adequate contraceptive methods should not be excluded.

(15) The Case Report Forms used should be as uniform as possible among all the various Celgene studies for recording the same information across studies.

(16) A partial response to treatment, defined as either the absence of acutely inflamed lesions (old lesions may still be resolving) OR a complete resolution of fever, but not both, is not considered a success for regulatory purposes.

The following Efficacy Outcome Categories are suggested.

OUTCOME CATEGORIES	Tenderness (T) Induration (I) Erythema (E)	Presence of Fever
Total Remission	NONE	NONE
Near total Remission	90%-99% of lesions without (T),(I)&(E)	NONE
Improvement	75%- 89% of lesions without (T),(I)&(E)	NONE
Partial Improvement	25%- 74% of lesions without (T),(I)&(E)	+/-
Minimal Improvement	0%- 24% of lesions without (T),(I)&(E)	+/-

Total and Near Total Remission categories are required to demonstrate efficacy.

Changes To Amended Protocol Dated July 7, 1996 and Revised Labeling (Submitted February 3, 1997:

(17) Protocol changes were made in response to

Division's query regarding end points that prevent irreversible morbidity. These changes are not consistent with the Division's current understanding of thalidomide's properties based on the recent data submitted by Celgene. Final modifications, excluding the safety issues as outlined above, should be the decision of the Sponsor and must be data driven. The safety issues raised need immediate attention, justification or clarification.

b. E-001

(1) The protocol needs to establish treatment failure criteria. The protocol has no stated "maintenance treatment failure" criteria or "refractory" criteria.

(2) The actual acute flare dosing schedule should be provided, and ENL severity criteria should be characterized for dosing at the upper limits of 300 mg or 400 mg with thalidomide.

(3) Patients requiring concomitant medications to control ENL symptoms should be considered a treatment failure.

(4) The rationale for three month dose stabilization with the Celgene thalidomide product should be provided.

(5) Efficacy end points should be clearly defined.

(6) The trial should have separate protocols with clearly defined endpoints (e.g., inpatient, outpatient, acute dosing, maintenance dosing, etc.). The protocol may need to be redesigned to better assess the dose response for safety and efficacy.

(7) The protocol should establish disposition categories, i.e., terminated, discontinued, disqualified, completed, etc.

(8) Protocol E-001 should address discontinuation of

thalidomide, should thalidomide induced neuropathy occur.

(9) A continuation study should be designed to follow and monitor the development and frequency of thalidomide-induced neuropathy.

Additional comments:

(10) Please provide criteria for "stable" patients (page 10, Protocol E-001) under Thalidomide Tapering.

(11) Acute and chronic use protocols are needed describing:

a) criteria for adequate control of the ENL reaction,

b) the use of oral steroids when thalidomide alone does not adequately control ENL, and

c) treatment failure criteria for thalidomide.

(12) The protocol amendment for Protocol E-001 should provide criteria for presumptively differentiating thalidomide induced neuropathy from the disease induced neuropathy in "chronic use" patients.

(13) The management of neuritis should be addressed in Protocol E-001.

(14) Please provide "enrollment logs" for all ongoing clinical studies that identify which screened patients qualified for study enrollment and which patients did not qualify (and why) for study enrollment.

(15) Submit a four-month safety update which includes updated data from studies E-001, E003/1P/Ext and E-003/P.

(16) Axillary temperatures for monitoring fever are unacceptable for clinical trials. Oral temperature recordings are required.

13. *Forward your proposals regarding patient information brochures, special packaging provisions (i.e., blister packaging, logos), pregnancy registry, pregnancy prevention programs, and labeling strategies for review.*

14. We understand that you may have questions, desire clarification, or wish to discuss these issues after reviewing these comments. We look forward to meeting with you.

Should you have any questions concerning this application, please contact:

Kevin Darryl White, M.B.A.
Project Manager
Telephone: (301) 827-2020

Sincerely yours,

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental
Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

DUPLICATE

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
Tel 908-271-1001
Fax 908-271-4184

Jonathan Wilkin, M.D. Director
Division of Dermatologic and Dental Drug Products
HFD-540
Center for Drug Evaluation and Research
Attn: Document Control Room
Corporate Building 9201
Corporate Boulevard
Rockville, MD 20857

1 April 1997

BZ
NDA ORIG AMENDMENT

NDA 20-785
Synovir Capsules (Thalidomide Capsules) 50 mg
Chemistry, Manufacturing and Controls
Amendment to a Pending New Drug Application

Dear Dr. Wilkin:

Reference is made to the NDA 20-785 for Synovir® Capsules (Thalidomide Capsules), 50 mg, submitted on December 20, 1996 and the pre-submission submitted on October 24, 1996. An amendment was made on February 25, 1996 updating stability information with a statistical trend analysis of [ ] stability data.

On March 7, 1997, Dr Wilson DeCamp, Chemistry Team Leader in your division, called and requested that we provide updated stability tables with the [ ] data used in the statistical evaluation. He also said the statistician requested a diskette with the data used for the SAS program. Enclosed you will find the updated tables for the batches used in the statistical analysis and a diskette with the SAS data.

If there are any questions regarding this amendment, please contact me at (908) 271-4137.

REVIEWS COMPLETED
CSO ACTION
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

Sincerely,

Norma P. Loeffler
Associate Director, Regulatory Affairs, Immunotherapeutics

Enclosures (duplicate)
Desk Copy cover letter only: Dr. Wilson DeCamp, Chemistry Team Leader

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
APR 1 1997
MEGA DOC RM

Celgene

DUPLICATE

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
Tel 908-271-1001
Fax 908-271-4184

BZ

ORIG AMENDMENT

7 March 1997

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Jonathan Wilkin, M.D.
Director, Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Re: NDA 20-785
Thalidomide Capsules
Amendment to a Pending Application
Response to Reviewers' Requests

Dear Dr. Wilkin:

On 6 March 1997 Celgene Corporation received a teleconference call from Kevin Darryl White and Dr. Wilson DeCamp requesting a copy of the revised draft package insert for thalidomide on diskette and an update to the stability study analysis. In addition, Celgene received a second teleconference call from Kevin Darryl White and Dr. Susan Walker on 7 March requesting copies of clinical literature summaries from New Drug Application (NDA) 20-785 on diskette.

As requested, enclosed please find one diskette with the revised package insert, and one diskette with the clinical summaries from Study L-003 (Literature Review of the Efficacy of Thalidomide) and Study L-004 (Literature Review of the Safety of Thalidomide). All three documents are in WORD 7.0 on PC-compatible diskettes.

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EVALUATION AND RESEARCH

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The statistical analysis of the stability data is presently being carried out by [redacted]. An update of this analysis will be available as soon as available.

Please do not hesitate to contact me with any questions or additional comments.

Sincerely,

Steve Thomas -KDL

Steve Thomas, Ph.D.
Vice President, Pharmaceutical Development

Desk copies: Kevin Darryl White/cover letter with diskettes
Wilson deCamp, Ph.D./cover letter only
Susan Walker, M.D./cover letter only
Jonathan Wilkin, M.D./cover letter only

BIT
ORIG AMENDMENT

ORIGINAL

Celgene

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
Tel 908-271-1001
Fax 908-271-4184

REVIEWS COMPLETED

CBO ACTION:
☐ LET ☐ N.A.I. ☐ MEMO

CBO INITIALS DATE

6 March 1997

CENTER FOR DRUG EVALUATION AND RESEARCH
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Jonathan Wilkin, M.D.
Director, Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Re: NDA 20-785
Thalidomide Capsules
Information Amendment:
Responses to Reviewers' Comments

Dear Dr. Wilkin:

On 25 February 1997 Celgene Corporation received a teleconference call from Kevin Darryl White, Dr. Brenda Vaughan and Dr. Susan Walker. Dr. Vaughan and Dr. Walker requested additional information and clarification regarding Studies L-001 and L-002. Preliminary responses were provided via facsimile to Kevin Darryl White on 26 February 1997. A copy of the facsimile is provided in Attachment 1. In the balance of this letter, each question is restated, followed by Celgene's response.

Study L-002

1. Dr. Susan Walker asked whether Celgene can cross-reference the patient numbers with the location of the source documents? If so, could these data be provided as a data dump? If it is too difficult to provide the complete data, can Dr. Walker provide the selected patient numbers, and Celgene in return provide the location of the source documents?

   A complete listing of patients with corresponding study sites is provided in Attachment 2. Please note that the patient numbers used for purposes of report generation do not correspond to the patient's medical record number at the site. If more information is needed, Celgene has requested that Dr. Walker clarify

whether the source documents of interest are the 1-page Case Report Forms (CRF) for the Annual Report or whether she is referring to the patient medical records which are retained at the individual sites.

2. Currently there are 20 columns on the L-002 SAS data set, and therefore not all data can be displayed on one page. Dr. Walker requested that the data set be reprinted so that only seven columns appear (fitted to the page). The column headings are OBS, Line Num, Pt ID2, Entry Year, Diagnosis Date, Start Date, Dosage and Response.

   The requested listing is provided in Attachment 3.

3. Dr. Walker requested that Celgene explain the difference between Start Date and Entry Year.

   As previously stated in the facsimile of 26 February 1997, the Start Date is the date that the patient started thalidomide treatment. The Entry Year refers to the reporting year for the IND 11,359 Annual Report. Physicians submit one-page CRFs annually (generally in April); these reflect treatment in the preceding calendar year. For example, CRFs submitted to Carville in April 1995 correspond to Entry Year 1994.

4. Dr. Walker inquired whether it is possible to determine treatment start and stop dates.

   As can be seen on the sample CRF (Attachment 4), the Principal Investigator records the date that thalidomide was started in item 8 (Start Date). Whether or not the patient is continuing treatment or thalidomide treatment was discontinued is recorded in item 15. These stop dates were not entered into the computerized database by Carville. Celgene has entered these data for the Entry Year 1992 to 1994 (the years for which CRFs are in-house). The listing of stop dates is provided in Attachment 5; the remaining patients continued on treatment at the end of the year.

Study L-001

5. Dr. Vaughan inquired whether there is a protocol for Study L-001? If so, she requested a copy.

   The clinical study was conducted at the inpatient infirmary of what is now called the National Hansen's Disease Center (NHDC) in Carville Louisiana under the direction of the Principal Investigator, Dr. Robert C. Hastings. Dr. Hastings has indicated that a protocol and randomization code were used in the conduct of the study but that all original records (other than a listing of all patients treated with thalidomide at NHDC and patient medical records) were lost when Dr. Hastings

moved from the NHDC to the University of Louisiana. Dr. Hastings further indicated that a complete description of the study protocol was published (Hastings, 1970) and is summarized in the study participation sheet inserted into the patient's medical record. He stated that he carried out the study according to the protocol. In cooperation with the company's efforts to analyze the study, Dr. Hastings provided Celgene access to the source medical records.

6. Dr. Vaughan asked how patients were randomized in Study L-001, primarily for Bottle A. She also inquired about randomization to Bottle B.

   Study L-001 was a double blind placebo controlled study of 4 days' treatment duration. As stated in the response to the previous question, the randomization code has been lost. Dr. Hastings indicated that a randomization code was created and that numbered bottles designated, 'Bottle A', were filled with either thalidomide 100 mg or placebo capsules. 'Bottle B' was filled with the alternative treatment. That the investigator, other personnel, and patients were blind to the contents of 'Bottle A' until after the determination of treatment response is clear from reading the Progress notes.

7. Dr. Vaughan noted that some patients continued on 'Bottle A' and that some patients switched to 'Bottle B'. She inquired as to what guidance was given for deciding when to switch between the two bottles.

   As stated above, double blind dosing was initiated with 'Bottle A' for all patients. Patients were to be observed daily, and patient temperatures were to be taken four times daily. Patients were to receive double blind study drug for 4 days, at which time response and need for continued treatment were to be evaluated. Patients were to be examined for fresh ENL lesions and temperatures on the morning of the fourth day of the double blind study in order to assess the effectiveness of the treatment. Patients were either continued on treatment for 4 additional days in the event of response or switched to 'Bottle B' in the event of treatment failure. The physician's rationale for switching is stated in the progress notes.

   There were 24 treatment courses with 'Bottle A' (23 patients). Of these 24 treatment courses, 13 patients showed a response to 'Bottle A', 10 responded to thalidomide treatment, 3 responded to placebo. Of these 13 responders all 13 patients were afebrile with no fresh lesions on the fourth day of treatment; 12 patients continued on blinded 'Bottle A' and 1 patient receiving thalidomide was switched to 'Bottle B'.

   Eleven patients failed to respond to 'Bottle A' treatment, 9 of these patients were receiving placebo treatment, and 2 patients were receiving thalidomide. Of these 11 patients, 10 were switched to 'Bottle B', (1 patient after 6 days rather than 4 days). One patient was afebrile on the fourth day of 'Bottle A' treatment with

no new lesions, but was considered a failure due to the fact that the patient's average temperature for the 4 days of treatment had been 102°F; this patient remained on blinded 'Bottle A' treatment.

NDA Outstanding Issues

8. Kevin Darryl White requested that Celgene submit a debarment statement.

   A signed debarment statement will be provided shortly.

Please let me know if you have any more questions.

Sincerely,

Steve Thomas, Ph.D.
Vice President, Pharmaceutical Development

Desk Copies:

Brenda Vaughan, M.D.
Susan Walker, M.D.
Kevin Darryl White

ORIGINAL

Celgene Corporation
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Warren, New Jersey 07059
Tel 908-271-1001
Fax 908-271-4184

B2

ORIG AMENDMENT

Jonathan Wilkin, M.D. Director
Division of Dermatologic and Dental Drug Products
HFD-540
Center for Drug Evaluation and Research
Attn: Document Control Room
Corporate Building 9201
Corporate Boulevard
Rockville, MD 20857

February 25, 1997

NDA 20-785
Synovir Capsules (Thalidomide Capsules) 50 mg
Chemistry, Manufacturing and Controls
Amendment to a Pending New Drug Application

Dear Dr. Wilkin:

Reference is made to the NDA 20-785 for Synovir® Capsules (Thalidomide Capsules), 50 mg, submitted on December 20, 1996 and the pre-submission submitted on October 24, 1996.

In the pre-submission, Celgene committed to submitting a statistical trend analysis for the drug product, Thalidomide Capsules, 50 mg. We herewith enclose the statistical analysis based on the currently avalailable data, [ ]

Based on the evaluation, we are proposing [ ] expiration date. However, since the 95 percent confidence intervals are large on the basis of only [ ] worth of data, we intend to update the statistical analysis when additional room temperature data is available.

If there are any questions regarding this correspondence, please contact me at (908) 271-4137.

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
GSO INITIALS DATE

Sincerely,

Norma P. Loeffler
Associate Director, Regulatory Affairs, Immunotherapeutics

Desk Copy: Dr. Wilson DeCamp, Chemistry Team Leader

ORIGINAL

Celgene

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
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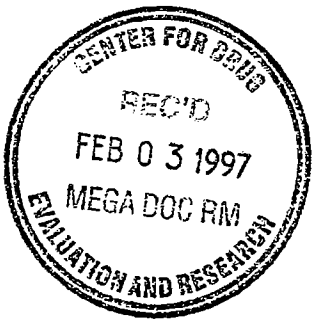
NDA ORIG AMENDMENT

3 February 1997



Jonathan Wilkin, M.D.
Director, Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

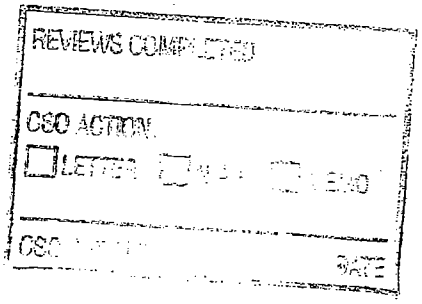
Re: NDA 20,785
Thalidomide capsules
(Synovir™)
Preliminary Report:
Thalidomide in the Treatment of
ENL With or Without
Associated Neuritis

Dear Dr. Wilkin:

Please refer to the New Drug Application (NDA 20-785) submitted 20 December 1996 for thalidomide capsule in the treatment of erythema nodosum leprosum. Please also refer to your facsimile dated 13 January 1997 and Celgene Corporation's response dated 21 January. As requested, please find enclosed the following:

- A preliminary report that elaborates on the trial course of response to thalidomide and includes case narratives for the treatment of patients with ENL-associated neuritis.
- Revised product labeling.
- Protocol amendment for Study E-003/P revising the primary endpoints to include symptoms that result in irreversible debility.

The preliminary report is being submitted in draft since the case narratives have been sent to the investigators for review. When these reviews are finalized, the individual study reports submitted to the NDA 20-785 will be amended.



I would be grateful if you could respond to the suitability of this information for your review purposes at your earliest convenience. If you have further comments or questions, I can be reached at (908) 805-3914.

Sincerely,

Steve Thomas -KSL

Steve Thomas, Ph.D.
Vice President, Pharmaceutical Development

ORIGINAL

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28 January 1997

NEW CORRESPONDENCE

Jonathan Wilkin, M.D.
Director, Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Re: NDA 20-785
Thalidomide capsules
(Synovir™)
General Correspondence
and Meeting Minutes

Dear Dr. Wilkin:

With respect to our recent discussions relating to the filing of NDA 20-785 I am enclosing a position paper formulated by Alan Kaplan of Kleinfeld, Kaplan and Becker. I hope this document assists the Division of Dermatologic and Dental Drug Products in its deliberations on this matter.

The contents of this submission are as follows:

1) This cover letter and FDA form 356h.

2) Position paper of Mr. Alan Kaplan with enclosures.

   Exhibit A-a copy of correspondence from Dr. Wilkin to Celgene dated 13 January 1997.

   Exhibit B-minutes of a meeting held on 17 January 1997 together with Celgene proposals addressing points raised in the meeting. (This was previously submitted to the Agency by facsimile 22 January 1997).

Please feel free to call me with any questions.

Sincerely,

Steve Thomas -tbk
Steve Thomas, Ph.D.
Vice President, Pharmaceutical Development

ORIGINAL

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7 Powder Horn Drive
Warren, New Jersey 07059
Tel 908-271-1001
Fax 908-271-4184

23 January 1997

BZ
NDA ORIG AMENDMENT

Jonathan Wilkin, M.D.
Director, Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Re: NDA 20,785
Thalidomide capsules
(Synovir™)
Volume 3.1

Dear Dr. Wilkin:

Pursuant to 21 CFR Part 314, please find enclosed an amendment, Volume 3.1, to NDA 20-785 for thalidomide capsules (Synovir™) which was submitted on 20 December 1996. This amendment is a revision of the NDA summary volume (Section 2, Volume 2.1). The revision contains the Annotated Package Insert and changes to the Overall Table of Contents. Twelve desk copies were previously delivered to the Division on 8 January.

Please feel free to call me with any questions.

Sincerely,

Steve Thomas, Ph.D.
Vice President, Pharmaceutical Development

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JAN 2 3 1997
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REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
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21 January 1997

Jonathan Wilkin, M.D.
Director, Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Re: NDA 20,785
Thalidomide capsules
Subpart E designation
Meeting minutes

Dear Dr. Wilkin:

I would like to thank the Division of Dermatologic and Dental Drug Products and other FDA representatives for providing Celgene with the opportunity to meet and discuss the issues described in your facsimile of 13 January 1997. A copy of the minutes of this meeting and a copy of your 13 January facsimile are attached. I thought it would be useful to outline the approach Celgene Corporation will take to address your concerns so that the Division will have a clear understanding of the quantity and type of supplementary data which will be submitted to meet the February 2 deadline that you set. In addition, as requested by the Division, the proposed label and the endpoints in the Phase 4 trial will be modified. We request that the Division comment on this approach during the telephone conference call scheduled for 22 January at 2:30 pm.

SUITABILITY OF THE APPLICATION FOR REVIEW UNDER 21 CFR 312 SUBPART E

During the discussions with the Division on 17 January Celgene was presented with the task of identifying subsets of ENL patients in the clinical databases with symptomatology such as, but not limited to, "inflammation of the peripheral nerves (neuritis), testes (orchitis), anterior chamber of the eye (uveitis) or kidneys (nephritis) which if left untreated could result in severe irreversible morbidity." Furthermore, it was clearly stated that failure of Celgene to identify such patient subsets would render review of the application under the Subpart E regulations inappropriate and would consequently result in a Refusal-to-File action by the Agency. Celgene has consulted with its Investigators on this issue and has also undertaken a preliminary review of data held at the company to assess the likely availability of data which could assist the Division in coming to a decision on its ability to file the application.

Background

Erythema nodosum leprosum (ENL) is an acute reaction occurring in patients with lepromatous and borderline lepromatous leprosy. The role of thalidomide in treating the acute manifestations of ENL, such as fever, cutaneous lesions, and associated systemic symptoms including neuritis, orchitis, uveitis, nephritis, *etc.* is well established. In many patients ENL is a chronic condition that can result in serious debility and irreversible morbidity when untreated or inadequately treated. Indeed in many leprosy patients this reaction can be the primary cause of deformity and disability. Patients with chronic ENL can ultimately become bedridden, unable to work, and hence seriously and irreversibly disabled psychologically and socioeconomically. Since ENL is a generalized systemic disease, serious physical disabilities can result in all organs and tissues affected. The most notable and commonly involved organs are the peripheral nerves, skin, eyes, testes, and kidneys. The literature describing untreated reactions of leprosy, prior to the implementation of steroid use in the 1950s, describes progression to debilitating and ultimately irreversible morbidities. Renal failure resulting in death was the most serious sequela of the disease. Deformity and loss of extremities was common, and blindness was also a possibility. With the advent of chronic corticosteroid therapy, effective treatment of ENL was available but presented many patients with the choice of enduring serious morbidity from corticosteroids or from their underlying ENL. Since Dr. Sheskins' successful first use of thalidomide in 1965 to control painful neuritis and other symptoms associated with ENL, multiple well controlled studies have testified to the efficacy and relative safety of thalidomide both in the context of concomitant corticosteroid usage [Pearson and Vedagiri, 1969; Waters, 1971] and as monotherapy [Hastings et al., 1970; Iyer et al., 1971; Sheskin and Convit, 1969]. As a result thalidomide became the agent of choice for the control of moderate to severe ENL as recommended by the World Health Organization (WHO). Several authorities attest to a decrease in the seriously debilitating outcomes, both associated with ENL and its complications and corticosteroid use. For example, as stated by Dr. Hastings in his seminal textbook on leprosy, "Thalidomide has been responsible for a huge decrease in permanent disability, including deformity, in leprosy patients."

Dr. Hastings at the United States Public Health Service (USPHS) hospital in Carville, Louisiana was one of the first investigators in the United States to use thalidomide in the treatment of ENL. In initial open label and single blind studies, and a subsequent double blind placebo controlled trial (Study Report L-001), he demonstrated that early intervention with thalidomide, occasionally in the presence of concomitant steroids, halts and reverses the acute symptoms of ENL which historically would have led to irreversible morbidity. Authorization by FDA of the USPHS Investigational New Drug application (IND 11,359) made thalidomide available to US Hansen's disease patients with ENL under a treatment protocol which enrolled over 1300 patients between 1978 and 1994. As a consequence of the efficacy of thalidomide seen in the drug's usage under IND 11,359, the severe irreversible morbidity previously seen in uncontrolled ENL patients or those ENL patients unable to tolerate high dose or chronic steroids has become extremely rare.

Dr. Srinivasan, the statistical reviewer, then listed his requests. He stated that he had questions about the identification of the variables in the L-002 dataset in order to be able to merge the datasets. Dr. Kook provided him with annotated case report forms for both this study and the progress report for Study E-003/P; she also indicated that she would provide him with a contact number for Bruce Sheppersen who created and analyzed the SAS dataset. Dr. Srinivasan then stated that he would like to be able to analyze Study L-002 to determine the time course to response. Dr. Kook indicated that because of the way the data were collected, using start of therapy and time of the report to calculate time to response was misleading. Reporting by investigators was done on an annual basis when the Annual Report to the Investigational New Drug application was due, and had no temporal relation to the onset of response; onset of response was not requested in the case report forms. She stated that one possibility could be to categorize patients in a given reporting year by the duration of time they had been on thalidomide and to look at the proportions of patients who responded, for example, by month. Dr. Srinivasan requested the SAS dataset for Study L-001. Dr. Kook responded that the data are in a Paradox database, and Celgene had previously inquired whether FDA had the ability to handle this program. Dr. Harkins indicated that a Paradox database should be sufficient.

Dr. Bashaw, the pharmacokinetic reviewer, stated that he had one major question. He wanted to know the link between the Celgene formulations and the "clinical trials formulations". Dr. Thomas replied that bioequivalence of the Celgene formulation used in Celgene-sponsored clinical trials, the proposed Celgene commercial formulation (which is also used in the ongoing study E-003/P), and the Tortuga formulation was studied. The latter formulation is that used most recently by Carville, and therefore represents the formulation that patients in Study L-002 have received in recent years. He further stated that a Celgene-sponsored trial is ongoing that clinically evaluates the conversion of patients from the Tortuga formulation to the Celgene formulation. In response to a query by Dr. Wilkin, Dr. Bashaw confirmed that this was not a filability issue, but rather a request for clarification. He then requested that information describing the steady state pharmacokinetics of thalidomide be available at the time of approval. Dr. Thomas indicated that Celgene is in the process of collecting these data, but that since this is the first time that FDA has requested these data prior to approval, he would need to make inquiries regarding the time frame for the availability of these data.

The meeting concluded at 10:30 am. Dr. Wilkin summarized by stating the it was critical that the requirements for Subpart E be met. Specifically, the ongoing/planned protocol(s) and the labeling must be modified to incorporate endpoints that reflect serious or irreversible morbidity and Celgene should find evidence in Study L-001 or Study L-002 that supports thalidomide's effectiveness in treating and preventing irreversible morbidity. Whether or not thalidomide is labeled for adjunctive therapy will be dependent on whether or not the subset of patients identified is receiving monotherapy.

Both Drs. Wilkin and Weintraub stated that FDA wants to work with Celgene to resolve these issues. If data are sent by facsimile, they will be reviewed promptly. A follow-up telephone conference call was scheduled for Wednesday 22 January at 2:30 PM. Celgene confirmed that the telephone number for Bruce Shepperson (for answering questions pertaining to the Study L-002 database) and Paradox diskettes for the Study L-001 database would be delivered to Kevin Darryl White, the project manager.

ORIGINAL

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
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Fax 908-271-4184

Jonathan Wilkin, M.D. Director
Division of Dermatologic and Dental Drug Products
HFD-540
Center for Drug Evaluation and Research
Attn: Document Control Room
Corporate Building 9201
Corporate Boulevard
Rockville, MD 20857

January 20, 1997

NDA 20-785
Synovir Capsules (Thalidomide Capsules) 50 mg
Chemistry, Manufacturing and Controls
General Correspondence

NEW CORRESPONDENCE

Dear Dr. Wilkin:

Reference is made to the NDA 20-785 pre-submission for Synovir® Capsules (Thalidomide Capsules), 50 mg, submitted on October 24, 1996. This correspondence concerns the statistical evaluation of the stability data for Thalidomide Capsules.

In the pre-submission, Celgene committed to submitting a statistical trend analysis for the drug product, Thalidomide Capsules, 50 mg. On January 9, 1997, Dr. Wilson DeCamp, Chemistry Team Leader in your division, contacted Dr. Steve Thomas of Celgene and inquired about the status of the evaluation and the time frame for submission.

A conversation followed on January 16, 1997 between Dr. DeCamp, Mr. Darrell White, Project Coordinator in your division and the undersigned. After discussion of the data which are currently available, it was agreed that Celgene could postpone the submission of the analysis until we had obtained the [redacted] data without risking a "refusal-to-file". These data will be submitted to the NDA by February 28, 1997.

If there are any questions regarding this correspondence, please contact me at (908) 271-4137.

REVIEWS COMPLETED

CSO ACTION
☐ LETTER ☐ N.A.L. ☐ MEMO

CSO INITIALS DATE

Sincerely,

Norma P. Loeffler
Associate Director, Regulatory Affairs, Immunotherapeutics

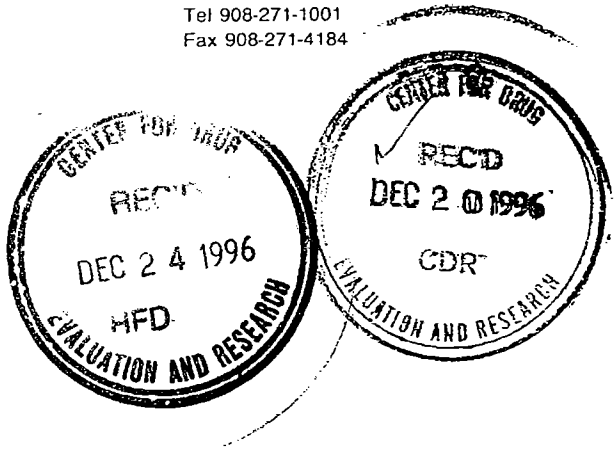
CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JAN 22 1997
HFD-

Desk Copy: Dr. Wilson DeCamp, Chemistry Team Leader

ORIGINAL

NEW DRUG APPLICATION

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
Tel 908-271-1001
Fax 908-271-4184



20 December 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Central Documents Room
12229 Wilkins Avenue
Rockville, MD 20852

Re: NDA 20-785
Thalidomide Capsules
(Synovir™)
Submission of New Drug
Application
Volumes 2.1-2.49

Ladies and Gentlemen:

Pursuant to 21 CFR Part 314, please find enclosed the submission of New Drug Application , 20-785 for thalidomide capsules (Synovir™). The Chemistry, Manufacturing and Controls section and the Methods Validation portions of the application (volumes 1.1-1.16) were pre-submitted 24 October 1996. The proposed indication is the acute treatment of erythema nodosum leprosum (ENL) as well as the maintenance therapy for prevention and suppression of ENL recurrence. The proposed use has been granted Orphan Drug Designation. Celgene Corporation has been granted a waiver of the NDA application fee (see enclosed).

Celgene Corporation is submitting this New Drug Application for thalidomide in the treatment of erythema nodosum leprosum (ENL). Synovir has been granted Orphan Drug status for use in this indication. The development program has been undertaken in consultation and agreement with the Food and Drug Administration, Division of Dermatologic and Dental Drug Products. During the course of several meetings, the severity of ENL and the difficulty of undertaking controlled clinical trials in this indication have been acknowledged. Since ENL is a seriously debilitating condition, and potentially life threatening in its most severe form, patients require continued access to

treatment with thalidomide, widely acknowledged to be the treatment of choice in this indication. At a recent FDA Advisory Committee meeting, on 8 November 1996, Deputy Commissioner Mary Pendergast stated the lack of GMP compliance associated with current supplies of imported drug is a serious public health concern which this NDA seeks to rectify.

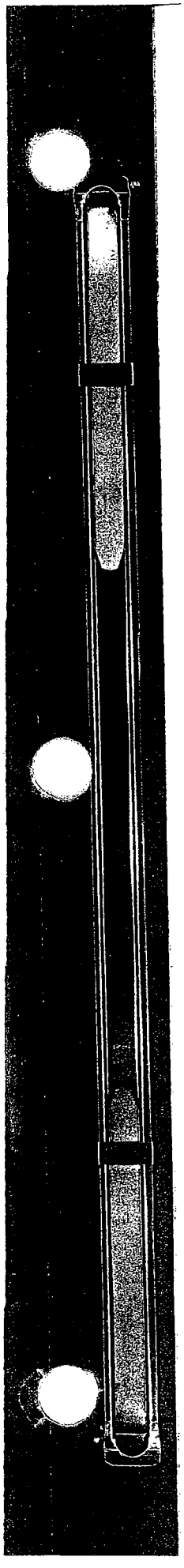
The data submitted in this NDA demonstrate that thalidomide is effective in the acute treatment of ENL when used in doses of 100 to 400 mg/day. The ongoing trial in the Philippines supports the consistent reports of others that efficacy is approximately 90%, with resolution of signs and symptoms within 2 to 5 days. These patients were seriously ill with fever, extensive lesions, and systemic symptoms. No patient received steroids, and only 1 patient was receiving antimicrobial therapy. Thalidomide is also effective in the treatment of seriously ill patients who have previously been steroid dependent, and who are receiving concomitant antimicrobial therapy, as for example, in the study conducted by Dr. Hastings in the United States. Celgene has conducted a review of the medical records pertaining to this study and has confirmed the published findings. Thalidomide has also been demonstrated to be effective in the continued suppression of the recurrence of ENL signs and symptoms. Both ongoing Celgene-sponsored trials and the extensive published literature support the use of thalidomide in maintenance doses of 50 to 300 mg/day for control of ENL.

Thalidomide has also been demonstrated to be well tolerated in this indication. Extensive nonclinical studies failed to identify any additional risks not already known from thalidomide's extensive clinical use.

Please address any questions regarding NDA 20-785 to Dr. Steve Thomas, 908 805 3914.

Sincerely,

Steve Thomas, Ph.D.
Vice President, Pharmaceutical Development



Celgene

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
Tel 908-271-1001
Fax 908-271-4184

24 October 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, MD 20852

Re: NDA 20-~~758~~ 785
Thalidomide Capsules (Synovir™)
Pre-NDA Submission of Chemistry, Manufacturing, and Controls Data
Volumes 1.1 - 1.16

Ladies and Gentlemen:

Pursuant to 21 CFR Part 314, please find enclosed the presubmission of the Chemistry, Manufacturing and Control sections (Sections 3 and 4) of New Drug Application (NDA) 20-758 for Thalidomide Capsules (Synovir™). Thalidomide is indicated for the treatment of erythema nodosum leprosum, an inflammatory reaction occurring in patients with Hansen's disease. Thalidomide for use in this indication has been granted Orphan Drug Designation and a User Fee waiver has been requested.

These Chemistry, Manufacturing, and Controls (CMC) data are being submitted in anticipation of the inspection of [ ] the drug product manufacturing facility in the [ ]. Therefore, an additional desk copy is provided for Dr. Wilson De Camp, to be forwarded to the International Operations Branch. This letter also serves to certify that an exact copy has been forwarded directly to the attention of Regina Brown in the Newark District Office (Parsippany).

This pre-NDA submission of the CMC data is complete with the following three exceptions. First, please be advised that a commercial packager has been identified, but detailed descriptions of the configuration and packaging operations for the commercial product are not yet available. The materials to be used will be consistent with the packaging used in clinical trials. Container labeling is also provided in draft. Second, the lot numbers of samples to be provided for method validation will be identified in the future. Finally, additional stability data for drug substance and drug product will be submitted on an ongoing basis while the NDA is under review.

Please address any questions or comments regarding the CMC sections of the NDA to the undersigned, Dr. Steve Thomas, at 908 805 3914.

Sincerely,

Steve Thomas, Ph.D.
Vice President, Pharmaceutical Development

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Office of the Commissioner
5600 Fishers Lane
Room 14-105, (HF-7)
Rockville, MD 20857
301-827-3390

December 19, 1996

Steven Thomas, Ph.D.
Vice President
Pharmaceutical Development
Celgene Corporation
7 Powder Horn Drive
Warren, NJ 07059

Re: Prescription Drug User Fee Act of 1992
Waiver Request
Our file: WR 97.005

Dear Dr. Thomas:

This letter responds to your letter on behalf of Celgene Corporation, (Celgene), dated September 6, 1996, requesting a waiver of the application fee and annual product fee assessed under the Prescription Drug User Fee Act of 1992, 21 U.S.C. § 379g, et. seq., upon the submission of the marketing application (NDA 20-785) for Synovir (2-Phthalimidoglutaramide). For the reasons described below, the Food and Drug Administration grants the waiver of the application fee requested. FDA cannot, however, consider a waiver of the annual product fee in the absence of an approved product, thus Celgene should submit a waiver request when an annual product fee is assessable.

Celgene anticipates submitting a marketing application for Synovir in the near future. During fiscal year (FY) 1997, the User Fee Act requires persons submitting marketing applications to pay an application fee of approximately $233,000, 21 U.S.C. § 379h (a)(1). Celgene requests a waiver of the application and product fees under two waiver provisions: first, that a waiver is necessary to protect the public health, 21 U.S.C. § 379h(d)(1); and second, that the fee is a significant barrier to innovation, 21 U.S.C. § 379h(d)(2).

In its waiver request Celgene states that Synovir is to be used in the acute treatment of erythema nodosum leprosum (ENL) as well as maintenance therapy for

prevention and suppression of ENL recurrence. FDA's Office of Orphan Product Development designated this product as an orphan pursuant to 21 U.S.C. § 360bb, et seq. Celgene received the Orphan Drug designation (95-907) for this use on July 25, 1995. According to Celgene ENL is a seriously debilitating and potentially life threatening complication of Hansen's disease and the use of Synovir in its treatment is necessary to protect the public health. Celgene also states that Synovir is recognized as the treatment of choice and there are no other approved sources of the drug in the United States. The OPD estimates that the population afflicted with ENL in the United States by the most conservative estimate would not exceed 7,500 cases; however, the OPD also states that in reality this number would be much less. Celgene estimates that the total number of patients receiving Synovir in a given year will not exceed 500.

In further support of its waiver request, Celgene states that it is a small publicly traded company and pharmaceutical development represents a new venture for Celgene. According to Celgene the company's sole revenue is derived from the sale of specialty chemicals and the company has no revenue generated from any marketed drugs. Celgene states that it has dedicated a large portion of the company's resources to researching and developing this drug so that it could be more readily available to patients. Celgene provides figures for FY 1995 that show recorded revenue of $ [ ] The figures provided by the company for the period January 1 through September 30, 1996 shows that Celgene has revenue of [ ] Celgene estimates that assuming 100% U.S. market penetration of Synovir, the annual revenue from the sale of the product would be approximately [ ] In addition, Celgene points out that patients with ENL typically have difficulty obtaining employment due to their condition, and the poor socioeconomic status of the target population will very likely affect the market price of the treatment.

Ordinarily, FDA will find that a waiver is necessary to protect the public health when two criteria are fulfilled. First, a person requesting a waiver must show that it is engaged in an activity that protects the public health. Second, a person requesting a waiver must show that a waiver is necessary to the continuation of the activity shown to protect the public health.

With respect to the first criterion, FDA concludes that Celgene's work to research, develop, and gain market approval of Synovir for treatment of patients with ENL, a seriously debilitating and potentially life threatening complication of Hansen's disease, is an activity that protects the public health. It is important to note that FDA need not conclude that an application is approvable or fileable in order to conclude that an entity is engaged in activity that protects the public health. A conclusion, for user

fee purposes, that an entity is engaged in activity that protects the public health indicates nothing about the ultimate approvability of the marketing application.

With respect to the second criterion, FDA concludes that Celgene has shown that a waiver is necessary to the continuation of activities that protect the public health. In applying the second criterion, FDA balances a variety of factors, including, but not limited to, the estimated patient population and projected revenue to be derived from sales of the product, and the total annual revenue of the entity, including any affiliates. Ordinarily, a waiver of a fee is not necessary because the revenue derived from sales of the drug product, the entity's gross annual revenue, or other factors, provide a sufficient basis for payment of the fee.

In this case, with respect to the second criterion, FDA notes that the patient population is small, approximately 7,500. In addition, FDA notes that Celgene's total current revenue is limited, [ ] of the year ending December 31, 1995, and approximately [ ] from January 1 through September 30, 1996) and the company expects to derive limited annual revenue of [ ] from the sale of Synovir. As explained in the Draft Interim Guidance Document for Waivers of and Reductions in User Fees, Attachment G to User Fee Correspondence 2, dates July 16, 1993, although there is no express threshold for a small entity, FDA generally considers an entity with less than $10 million in total annual revenue to be less likely to be able to continue to research, develop and market products that protect the public health while paying user fees.

Therefore, based on this combination of factors, FDA concludes that Celgene has demonstrated that a waiver is necessary to protect the public health. Accordingly, pursuant to 21 U.S.C. § 379h(d)(1), FDA grants Celgene a waiver of the application fee assessable upon submission of NDA 20-785.[1] Please include a copy of this letter in NDA 20-785.

Please note that as announced in User Fee correspondence 3, dated August 5, 1993, FDA plans to disclose information about is actions granting or denying waivers and reductions, consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.

[1] Because FDA is granting Celgene's request for a waiver on the ground that a waiver is necessary to protect the public health, 21 U.S.C. § 379h (d)(1), FDA need not consider whether a waiver is also justified under the barrier to innovation ground cited by Celgene.

If you have any questions, please contact Ms. Tracey Forfa of this office by E-mail at TForfa@Bangate.fda.gov or by telephone at 301-827-3390.

Sincerely yours,

Suzanne O'Shea

Suzanne O'Shea
Deputy User Fee Waiver Officer
Office of the Chief Mediator and Ombudsman

4 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling