CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-430

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-430
[RE-SUBMISSION]

Drug name:	THALOMID®
Generic name:	Thalidomide
Formulation:	50 mg, 100 mg and 200 mg capsules for oral administration
Adult Indication:	Multiple myeloma
Current Submission:	NDA-NME
Applicant:	Celgene Corporation 7 Powder Horn Drive Warren NJ 07059
OCP Division:	Division of Pharmaceutical Evaluation V (HFD-860)
OODP Division:	Division of Drug Oncology Products (HFD-150)
Submission Date:	22-Dec-2003, 13-May-2005, 23-Nov-2005
Primary Reviewer:	Roshni Ramchandani, Ph.D.
Team Leader:	Brian Booth, Ph.D.
Type of Submission:	Type 6 sNDA

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I. Executive Summary

Thalidomide was originally approved (in July 1998) for the acute treatment of cutaneous manifestations of moderate to severe Erythema Nodosum Leprosum as well as for prevention and suppression maintenance therapy (NDA 20-785). In 2003, the applicant submitted a new drug application seeking approval for thalidomide for the treatment of patients with multiple myeloma after failure of standard therapies. The Agency sent the applicant a non-approval letter (dated Oct 22, 2004) listing several deficiencies, comments and recommendations regarding their submission. The Clinical Pharmacology and Biopharmaceutics review also indicated several recommendations and comments that were included in the action letter.

The current re-submission is the applicant's response to the Agency's action letter, and includes the results of a randomized study (E1A00) conducted by the Eastern Cooperative Oncology Group (ECOG) comparing thalidomide + dexamethasone vs. dexamethasone in previously untreated multiple myeloma patients. No pharmacokinetic (PK) data was collected in this study. In addition, the applicant has deleted all data and reference to study UARK-98-0003, which was found to have several deficiencies and was deemed unacceptable for submission.

The applicant has also responded to the individual deficiencies, recommendations and comments provided by the Agency in their action letter. The applicant has either addressed or has submitted plans to address these recommendations. These plans are acceptable to the Agency.

A. Recommendations

The Office of Clinical Pharmacology (OCP) has reviewed the Clinical Pharmacology section of NDA ——— and finds it to be acceptable.

Revisions to Label:

The applicant has highlighted two areas in the CLINICAL PHARMACOLOGY section (changes are in blue):

1. Under **CLINICAL PHARMACOLOGY**
   Pharmacokinetics and Drug Metabolism

   Applicant's labeling

   Absorption
   The absolute bioavailability of thalidomide from THALOMID® (thalidomide) capsules has not yet been characterized in human subjects due to its poor aqueous solubility. However, the capsules are 90% bioavailable relative to an oral PEG solution.

   FDA proposed labeling

   The above statement included by the applicant is acceptable for inclusion in the label.

The data to support this was not included as part of this submission. It was submitted to the thalidomide IND 48,177, serial no. 084. This report was reviewed by the Agency and the results were found to be acceptable (Refer to submission dated sept 17, 2002, IND 48,177, serial no. 084).

2. Under **CLINICAL PHARMACOLOGY**
Pharmacokinetic Data in Special Populations

Applicant's labeling

Patients with Renal Insufficiency

[ ]

FDA proposed labeling

Rationale: The sponsor has not really conducted the studies in renally impaired patients and so it should be made distinctly clear that there is no dosage adjustment needed for patients on dialysis, provided the dialysis is performed 4-5 hours (following the Tmax) after ingestion of the drug.

Patients with Renal Insufficiency

The pharmacokinetics of thalidomide in patients with renal impairment have not been determined. In a study of 6 patients with end-stage renal disease, thalidomide (200 mg/day) was administered on a non-dialysis day and on a dialysis day. Comparison of concentration-time profiles on a non-dialysis day and during dialysis where blood samples were collected at least 10 hours following the dose, showed that the mean total clearance increased by a factor of 2.5 during hemodialysis. Because the dialysis was performed 10 hours following administration of the dose, the drug-concentration time curves were not statistically significantly different for days patients were on and off of dialysis. Thus no dosage adjustment is needed for renally-impaired patients on dialysis.

B. Phase IV Commitments

None.

C. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

There was no new clinical pharmacology information included in the re-submission. The following summary is repeated from the previous review (dated 22-Oct-2004).

The PK of thalidomide has been examined in several studies submitted with the original NDA for thalidomide, primarily following single doses in healthy volunteers, as well as studies in HIV-positive patients and Hansen's disease patients. Additional studies have been conducted by other investigators in oncology populations (Baidas et al., 2000; Figg et al., 1999; Fine et al., 2000). However, there are no PK studies of Thalomid® (thalidomide capsule formulation) in multiple myeloma patients.

The following PK characteristics of thalidomide have been obtained from the above studies:

Thalidomide is a racemic glutamic acid derivative. Thalidomide interconverts between the (R)- and (S)-enantiomers in plasma, with protein binding of 55% and 65%, respectively. After a single oral 200 mg dose of thalidomide (as the US-approved capsule formulation) in healthy volunteers, absorption is slow and extensive, resulting in a peak concentration (Cmax) of 1–2 mg/L at 3–4 hours after administration. The absorption lag-time was 30 minutes, the total exposure (AUC∞) was 18 mg • h/L, the apparent elimination half-life was 6 hours and the apparent systemic clearance was 10 L/h. Thalidomide pharmacokinetics was best described by a one-compartment model with first-order absorption and elimination. Because of the low solubility of the drug in the gastrointestinal tract, thalidomide exhibits absorption rate-limited pharmacokinetics (the 'flip-flop' phenomenon), with its elimination rate being faster than its absorption rate. The apparent elimination half-life of 6 hours therefore represents absorption, not elimination.

Thalidomide exhibits a dose-proportional increase in AUC at doses from 50 to 400mg. Because of the low solubility of thalidomide, Cmax is less than proportional to dose and Tmax is prolonged with increasing dose. Multiple doses of thalidomide 200 mg/day over 21 days cause no change in the pharmacokinetics, with a steady-state Cmax (Cssmax) of 1.2 mg/L. Multiple-dose studies in cancer patients show pharmacokinetics comparable with those in healthy populations at similar dosages. Age and sex have no effect on the pharmacokinetics of thalidomide, and the effect of food is minimal. Thalidomide does not alter the pharmacokinetics of oral contraceptives. The exact metabolic fate of thalidomide remains unknown, although it is believed to undergo non-enzymatic hydrolysis into a number of breakdown products. Previously submitted in vitro studies indicate that it is not metabolized by CYP enzymes. Following an oral dose, less than 1% of the dose is excreted unchanged in the urine. Thalidomide is thought to be mainly hydrolyzed and passively excreted. Barring any non-microsomal metabolism and barring the presence of any active metabolites that are eliminated renally, thalidomide disposition is not expected to be altered

in patients with impaired liver or kidney function. The clearance of thalidomide on non-dialysis days was not appreciably different from clearance in healthy volunteers.

A study of thalidomide administered to end-stage renal disease patients on hemodialysis showed that the amount of drug lost during a 3-hour dialysis was 20 mg. Thus, no dosage adjustments are needed for renally-impaired patients on dialysis. The reason for this loss being minimal may be related to the fact that dialysis was performed 8-10 hours after administration of the dose. Thus, the timing of dialysis relative to the administration of the dose is important, and as long as the dialysis is performed post peak, the loss of drug due to dialysis would be expected to be minimal.

II. QUESTION-BASED REVIEW

The current submission is a re-submission of the NDA for thalidomide, following the Agency's decision to issue a non-approval letter for the applicant's prior NDA supplement.
At the time of the initial review of the supplement, there were several recommendations and comments made from the clinical pharmacology perspective. The applicant has addressed the recommendations or has submitted plans for addressing the recommendations.
This review will focus on the applicant's responses and the submitted study reports. All other sections of the Question Based Review remain unchanged from the previous submission (submission date, October 2004).

Recommendations and comments to the Applicant at the time of the original submission and Applicant's Responses:

Recommendation 1

1. We recommend that you conduct the following studies to provide an adequate understanding of the metabolism and excretion of thalidomide. These data will provide the basis for deciding whether studies and/or dosage adjustment would be necessary in patients with organ dysfunction:

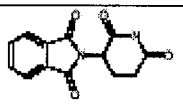
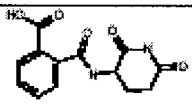
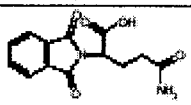
   In vitro hepatic metabolism:
   - We recommend that you perform *in vitro* studies in hepatic preparations to evaluate the potential influence of non-microsomal enzymes involved in the metabolism of thalidomide. If no other enzymes are detected then there is no need for a hepatic impairment study.

   Activity of metabolites:
   - We recommend that you identify the major metabolites of Thalidomide in urine of multiple myeloma patients. You should screen these metabolites *in vitro*/pre-clinically for pharmacological activity and if they are active you should plan to evaluate the pharmacokinetics of these metabolites. If there are no active metabolites identified in the urine, a renal impairment study will not be necessary."

   Applicant's Response:
   In vitro hepatic metabolism:
   The applicant has initiated an in vitro study (XBL 05631) to determine if there is any non-microsomal metabolism of thalidomide.

   Activity of metabolites:
   The applicant has indicated that three hydrolysis products of thalidomide have been detected in the urine or plasma of multiple myeloma patients in 2 recently published reports (Lu et al., 2003; Chung et al., 2004). These products were: *N*-(*o*-carboxybenzoyl)-glutamic acid imide, phthaloylisoglutamine and phthaloylglutamine. The hydrolysis products have been

synthesized and tested *in vitro* for pharmacological activity using three assays, each measuring a different aspect of thalidomide's known activity:
1) inhibition of tumor necrosis factor-alpha (TNF-α) production by human peripheral blood mononuclear cells (Sampaio et al. 1991 J. Exp. Med. 173:699), a measure of anti-inflammatory activity,
2) elevation of interleukin (IL)-2 production by T cells (Haslett et al. 1998 J. Exp. Med. 187:1885), a measure of T cell co-stimulation,
3) inhibition of migration of endothelial cells (Celgene Study Report 5239-92-5239-188), a measure of anti-angiogenic potency.

CC number	Compound Structure	Compound Name	MW	(1) TNF-α production at 50 μg/mL (% inhibition)	(2) IL-2 production at 50 μM (% elevation)	(3) VEGF-induced HUVEC migration (% inhibition)
2001		Thalidomide	258	52**	2	1 μM: 56%* 10 μM: 54%* 100 μM: 35%
1085		N-(o-carboxybenzoyl) glutamic acid imide	276	9.2	9	1 μM: 23% 10 μM: 26% 100 μM: 5.5%
1016		Phthaloylisoglutamine	276	5.9	11	1 μM: –4.6% 10 μM: 30% 100 μM: 39%
1007		Phthaloylglutamine	276	-14	11	1 μM: –7% 10 μM: 3.7% 100 μM: 35%
Conclusion				Only thalidomide is active	No compound is active	Thalidomide is more potent

* p≤0.05, **p≤0.01 vs. non-drug treated control

Results from these studies, summarized by the applicant in the above table, indicated that thalidomide inhibited TNF-α production by 52% at 50 μg/ml, while the hydrolysis products showed much lower levels of inhibition. Neither thalidomide nor the hydrolysis products showed significant elevations in T-cell IL-2 elevation. Thalidomide showed significant inhibition of human umbilical vein endothelial cells (HUVEC) induced by VEGF, ranging from 35-56% across thalidomide concentrations of 1-100 μM. In comparison, the hydrolysis products showed much lower (and statistically non-significant) levels of inhibition of HUVEC migration.

These results suggest that the hydrolysis products detected in the urine of multiple myeloma patients receiving thalidomide did not possess significant anti-inflammatory or anti-angiogenic activity.

Reviewer's Comment:

In vitro hepatic metabolism:

This is acceptable.

Activity of metabolites:
The above results cannot be conclusively interpreted since the fraction of the drug excreted in the form of hydrolysis products remains unknown. The applicant is conducting a PK study to determine the disposition of thalidomide and its hydrolysis products in plasma and urine of multiple myeloma patients,
The results of this study, along with complete study reports of the in vitro testing of pharmacological activity of the hydrolysis products, will provide the basis for determining the need for a renal impairment study.

Recommendation 2

Inhibition and Induction potential of thalidomide
To evaluate potential drug interactions, we recommend that you conduct *in vitro* studies to evaluate the inhibition and induction of thalidomide on any CYP enzymes at concentrations at least 10-fold higher than the expected Cmax following recommended doses in multiple myeloma patients."

Applicant's Response:
The applicant has initiated an in vitro inhibition study (XBL 05632) and an in vitro induction study (QPS 155N-0424).

Reviewer's Comment:
This is acceptable.

Recommendation 3

Pharmacokinetics in multiple myeloma patients:
The bioequivalence simulation approach does not demonstrate bioequivalence between the capsule (Celgene) and the tablet (Chemie Grunenthal) formulations.[1] The pharmacokinetics in multiple myeloma patients treated with the capsule remains unclear. We recommend that you examine thalidomide pharmacokinetics in multiple myeloma patients, either in a prospective study or in your ongoing phase 3 studies. This approach will allow the examination of exposure-response relationships for thalidomide, both for measures of toxicity and effectiveness."

Applicant's Response:

[1] In the prior submission, the applicant had submitted data on the PK of thalidomide in multiple myeloma, however the patients in that study were given a tablet formulation manufactured by Chemie Grunenthal. The applicant had performed simulations of the concentration-time profiles based on data obtained in healthy females using the Thalomid capsule formulation to demonstrate bioequivalence of the two formulations.

With regard to the bioequivalence simulation, the applicant has now completed a clinical study comparing the capsule and tablet formulations in healthy volunteers. Results indicated that the Cmax following the capsule was higher than after the tablet formulation, although the extent of absorption (AUC) was not statistically significant. The results of this study do not apply as the applicant is conducting a PK study in multiple myeloma patients using the commercial capsule formulation.

With regard to the PK of thalidomide in multiple myeloma patients, based on the Agency's prior recommendation, the sponsor is planning a 14-day study of thalidomide pharmacokinetics in multiple myeloma patients. The PK of thalidomide will be characterized following the initial dose and on day 14. The applicant also plans to isolate potential major metabolites in urine.

Reviewer's Comment:
The plan for a separate PK study is acceptable.

Comment 1

The half life of Thalidomide is 6 hours, and the regimens studied were based on QD dosing. This means that the drug was eliminated by the next dose. Effectiveness might be improved by alternate dosing (bid, tid). Are any other regimens being evaluated?"

Applicant's Response:
The applicant stated that there was no plan to evaluate alternate dosing regimens. The current regimen of giving the once-daily thalidomide capsules at bedtime was primarily due to the common side effects of drowsiness and somnolence caused by the drug.

Reviewer's Comment:
This is acceptable.

Comment 2

The applicant should consider the impact of the loss of the drug that might occur if dialysis occurs in the absorptive phase following a dose of thalidomide and should consider recommending that dialysis should not be done for at least 4 hours (post absorptive/peak period) post dose.

Applicant's Response:
The applicant stated that thalidomide is usually taken at bedtime while the hemodialysis is generally scheduled during the day, thus providing a natural separation of the absorption phase and the dialysis process, and greatly reducing the probability that dialysis would occur during the absorptive phase. Based on the results of the study in end-stage renal patients on dialysis, the loss of drug during the dialysis session that occurred at least 10 hours after dosing was minimal.

Reviewer's Comment:
The label language has been modified to reflect that dialysis was performed 10 hours following dosing.

A. General Attributes of the Drug

A1. What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Thalidomide originally received full approval in July 1998 for the acute treatment of cutaneous manifestations of moderate to severe Erythema Nodosum Leprosum (ENL) as well as for prevention and suppression maintenance therapy of the disease (NDA 20-785). The applicant is seeking approval for the treatment of patients with multiple myeloma

Following review of the prior supplement, the Agency sent the applicant a non-approval letter (dated Oct 22, 2004) listing several deficiencies, comments and recommendations regarding their submission. The Clinical Pharmacology and Biopharmaceutics review also indicated several recommendations and comments that were included in the action letter.
The current re-submission is the applicant's response to the Agency's action letter,

For answers to questions A2-A4, please refer to the clinical pharmacology review under NDA 21430 submission date 22-Dec-2003.

A2. What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

A3. What are the proposed mechanism(s) of action and therapeutic indication(s)?

A4. What are the proposed dosage(s) and route(s) of administration?

B. Clinical Pharmacology

For questions B1-B7, please refer to the clinical pharmacology review under NDA 21430 submission date 22-Dec-2003.

<u>General attributes</u>

B1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

B2. What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

B3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Exposure-response

B4. Is there a relationship between thalidomide exposure and effectiveness (response rates) in multiple myeloma patients?

B5. Is there a relationship between thalidomide exposure and incidence of adverse events including rash, constipation, peripheral neuropathy and sedation in multiple myeloma patients?

B6. Does this drug prolong the QT or QTc interval?

B7. Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Pharmacokinetics

B8. What are the PK characteristics of thalidomide?

(Summarized from NDA 21430 Supplement, submission date 22-Dec-2003)

The PK of thalidomide was examined in several studies that were submitted with the original NDA submission (for ENL). The studies included single dose studies in healthy volunteers, as well as studies in HIV-positive patients and Hansen's disease patients. Additional studies have been conducted by other investigators in oncology populations (Baidas et al., 2000; Figg et al., 1999; Fine et al., 2000). However, there are no PK studies of Thalomid® (thalidomide capsule formulation) in multiple myeloma patients. A recent study (Waage et al., 2004) examined the PK of thalidomide in multiple myeloma patients using a tablet formulation, however there are no data to determine if these tablets are bioequivalent to the applicant's capsule formulation.

The following PK characteristics of thalidomide were obtained from the above studies:

- Thalidomide is a racemic glutamic acid derivative. Thalidomide rapidly interconverts between the (R)- and (S)-enantiomers in plasma.
- The R- and S-isomers show protein binding of 55% and 65%, respectively.
- Following an oral dose, less than 1% of the parent drug is excreted unchanged in urine.
- Thalidomide is minimally metabolized by the liver, but appears to be spontaneously hydrolyzed into numerous products. The pharmacological activity and disposition of these products has not been clearly elucidated.
- After a single oral dose of thalidomide 200mg (as the US-approved capsule formulation) in healthy volunteers, absorption is slow and extensive, resulting in a peak concentration (Cmax) of 1–2 mg/L at 3–4 hours after administration, absorption lag time of 30 minutes, total exposure (AUC∞) of 18 mg • h/L, apparent elimination half-life of 6 hours and apparent systemic clearance of 10 L/h. Thalidomide pharmacokinetics are best described by a one-compartment model with first-order absorption and elimination.

- Because of the low solubility of the drug in the gastrointestinal tract, thalidomide exhibits absorption rate-limited pharmacokinetics (the 'flip-flop' phenomenon), with its elimination rate being faster than its absorption rate. The apparent elimination half-life of 6 hours therefore represents absorption, not elimination.
- Multiple doses of thalidomide 200 mg/day over 21 days cause no change in the pharmacokinetics, with a steady-state Cmax (Cssmax) of 1.2 mg/L.
- Thalidomide exhibits a dose-proportional increase in AUC at doses from 50 to 400mg. Because of the low solubility of thalidomide, Cmax is less than proportional to dose and tmax is prolonged with increasing dose.

For questions B9-B19, please refer to the clinical pharmacology review under NDA 21430 submission date 22-Dec-2003.

B9. What are the single dose and multiple dose PK parameters?

B10. How does the PK of thalidomide in healthy volunteers compare to that in patients?

B11. What are the PK characteristics of thalidomide in patients with cancers other than multiple myeloma?

B12. What are the characteristics of drug absorption?

B13. What are the characteristics of drug distribution?

B14. Does the mass balance study suggest renal or hepatic as the major route of elimination?

B15. What are the characteristics of drug metabolism?

B16. What are the characteristics of drug excretion?

B17. Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

B18. How do the PK parameters change with time following chronic dosing?

B19. What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

For questions C1-C4, please refer to the clinical pharmacology review under NDA 21430 submission date 22-Dec-2003. Additional issues regarding questions C2 and C3 are included below.

C. Intrinsic Factors

C1. What is the influence of age and gender on the PK of thalidomide?

C2. What is the influence of hepatic impairment on the PK of thalidomide?

The pharmacokinetics of thalidomide in patients with hepatic impairment have not been determined. However, since thalidomide is thought to undergo spontaneous, non-enzymatic hydrolysis, its metabolism would not be expected to be altered with hepatic dysfunction.

A recommendation was made to the applicant to perform *in vitro* studies in hepatic preparations to evaluate the potential influence of non-microsomal enzymes involved in the metabolism of thalidomide. If no other enzymes are detected then there would be no need for a hepatic impairment study.

C3. What is the influence of renal impairment on the PK of thalidomide?

The excretion of thalidomide is primarily non-renal; renal clearance of thalidomide was found to be less than 1% of the total clearance of the drug. Thalidomide is not extensively plasma protein bound. Therefore, renal insufficiency would not be expected to influence the disposition of thalidomide itself. However, the impact of renal dysfunction on the excretion of the putative metabolites of thalidomide is unknown.

A recommendation was made to the applicant to identify the major metabolites of thalidomide in urine of multiple myeloma patients and to screen these metabolites *in vitro*/pre-clinically for pharmacological activity. If these metabolites are active, the applicant should plan to evaluate the pharmacokinetics of these metabolites. If there are no active metabolites identified in the urine, a renal impairment study would not be necessary.

C4. What is the influence of other intrinsic factors on the PK of thalidomide?

For questions D1-D4, please refer to the clinical pharmacology review under NDA 21430 submission date 22-Dec-2003.

D. Extrinsic Factors

D1. What is the effect of food on the pharmacokinetics of thalidomide?

D2. Is there a significant pharmacokinetic interaction of thalidomide with oral contraceptives administered concomitantly in women?

D3. Based on the above (intrinsic and extrinsic factors), are there any recommendations for dosing adjustments for this population?

Other

D4. Are there any additional unresolved issues or omissions with regard to the evaluation of the PK and PD of thalidomide?

For questions E1, E3 and E4, please refer to the clinical pharmacology review under NDA 21430 submission date 22-Dec-2003.

E. Biopharmaceutics

E1. Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

E2. What is the relative bioavailability of the capsule formulation (Thalomid)?

The relative bioavailability of thalidomide capsules was determined in a previous study comparing the exposure following 2 x 50 mg thalidomide capsules vs. a solution of thalidomide in PEG 400 in healthy male and female volunteers. In this study, a 100 mg tablet formulation of thalidomide (manufactured by ———————) was also evaluated.
The study report was originally submitted to the IND for thalidomide (IND 48177 serial number 084, date 17-Sept-2002). This report was reviewed by the Agency and the results were found to be acceptable.

This was a single-dose, randomized, open-label, three-way crossover study in healthy male and female volunteers. Subjects received each of the following treatments in randomized order:

A: Thalidomide 100 mg dissolved in polyethylene glycol 400 (to a concentration of 100 mg/40 ml) administered with 240 ml of water.

B: Thalidomide 100 mg tablet (manufactured by ———————) administered with 240 ml of water.

C: Two Thalidomide 50 mg capsules (Thalomid®) administered with 240 ml of water.

Subjects received the treatment following an overnight fast. Serial blood samples were collected for measurement of plasma thalidomide concentrations following each treatment for up to 48 hrs. There was a 7 day washout between treatments.

Summary of Results:

- The PEG solution formulation resulted in an approximately 35% higher Cmax compared to the 100 mg tablet and the 50 mg Thalomid capsule formulations. The time of peak concentration occurred about 2 hours earlier for the solution formulation relative to the solid oral formulations.
- The mean AUCs were about 8-10% lower for the tablet and capsule formulations relative to the PEG solution.
- The 100 mg tablet and 2 x 50 mg capsule formulations were bioequivalent to each other with the 90% confidence intervals for the Cmax and AUC ratios falling within the pre-set 80%-125% boundaries.

- Safety data indicated that all treatments appeared to be safe when administered to healthy males. The most common adverse events were asthenia, dizziness and headache.

In conclusion, the bioavailability of the commercial 50 mg Thalomid capsule is approximately 90% relative to the PEG oral solution, based on AUC comparisons.

E3. What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

E4. How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

E5. What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?

None.

For questions F1-F5, please refer to the clinical pharmacology review under NDA 21430 submission date 22-Dec-2003.

F. Analytical Section

F1. How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

F2. Which metabolites have been selected for analysis and why?

F3. For all moieties measured, is free, bound or total measured? What is the basis for that decision, if any, and is it appropriate?

F4. What is the bioanalytical method that is used to assess concentrations of thalidomide?

F5. What are the figures of merit and performance characteristics for the methods used to assess concentrations of thalidomide and its metabolites?

III. Detailed Labeling Recommendations

The applicant has highlighted two areas in the CLINICAL PHARMACOLOGY section:

Agency additions are made in blue.

1. Under **CLINICAL PHARMACOLOGY**
Pharmacokinetics and Drug Metabolism

Applicant's labeling

Absorption
The absolute bioavailability of thalidomide from THALOMID® (thalidomide) capsules has not yet been characterized in human subjects due to its poor aqueous solubility.

FDA proposed labeling

The above statement included by the applicant is acceptable for inclusion in the label. The data to support this was not included as part of this submission. It was submitted to the thalidomide IND 48,177, serial no. 084. This report was reviewed by the Agency and the results were found to be acceptable (Refer to submission dated sept 17, 2002, IND 48,177, serial no. 084).

2. Under **CLINICAL PHARMACOLOGY**
Pharmacokinetic Data in Special Populations

Applicant's labeling

Patients with Renal Insufficiency

[

]

FDA proposed labeling

Rationale: The sponsor has not really conducted the studies in renally impaired patients and so it should be made distinctly clear that there is no dosage adjustment needed for patients on dialysis, provided the dialysis is performed 4-5 hours after ingestion of the drug.

Patients with Renal Insufficiency

The pharmacokinetics of thalidomide in patients with renal impairment have not

been determined. In a study of 6 patients with end-stage renal disease, thalidomide (200 mg/day) was administered on a non-dialysis day and on a dialysis day. Comparison of concentration-time profiles on a non-dialysis day and during dialysis where blood samples were collected at least 10 hours following the dose, showed that the mean total clearance increased by a factor of 2.5 during hemodialysis. Because the dialysis was performed 10 hours following administration of the dose, the drug-concentration time curves were not statistically significantly different for days patients were on and off of dialysis. Thus no dosage adjustment is needed for renally-impaired patients on dialysis.

24 Page(s) Withheld

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

__X__ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

B. CPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		Information
NDA Number	21-430	**Brand Name**	Thalomid
OCPB Division (I, II, III)	DPE-I	**Generic Name**	Thalidomide
Medical Division	HFD-150	**Drug Class**	Immunomodulatory, anti-proliferative
OCPB Reviewer	Roshni Ramchandani	**Indication(s)**	Multiple Myeloma
OCPB Team Leader	Brian Booth	**Dosage Form**	Capsules
		Dosing Regimen	200-800 mg QD
Date of Submission	5/13/05, 11/13/05	**Route of Administration**	Oral
Estimated Due Date of OCPB Review	5/14/06	**Sponsor**	Celgene Corporation
PDUFA Due Date	5/25/06	**Priority Classification**	P
Division Due Date	5/21/06		

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				

Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

Filability and QBR comments		
	"X" if yes	*Comments*
Application filable?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	**No new PK information submitted with this re-submission. Responses to OCP recommendations and comments to be discussed.**	
Other comments or information not included above		
Primary reviewer Signature and Date	Roshni Ramchandani	
Secondary reviewer Signature and Date	Brian Booth	

CC: NDA 21-430, HFD-850 (Electronic Entry), HFD-150 (Huntley),
HFD-860 (Booth, Rahman), CDR (Biopharm)

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/s/

Roshni Ramchandani
5/24/2006 05:30:37 PM
BIOPHARMACEUTICS

Brian Booth
5/24/2006 07:29:16 PM
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