CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-430

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-430

Celgene Corporation
86 Morris Avenue
Summit, NJ 07901

Attention: Megan Parsi
Director, Regulatory Affairs

Dear Ms. Parsi:

Please refer to your new drug application (NDA) dated December 22, 2003, received December 23,2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Thalomid (thalidomide) capsules, 50 mg, 100 mg, and 200 mg.

We acknowledge receipt of your submissions dated May 13, 2005; August 17, 2005; October 13 and 25, 2005. The May 13, 2005 submission constituted a complete response to our October 22, 2004 action letter.

We also acknowledge receipt of your submission dated November 1, 2005. This submission was not reviewed for this action. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and it is approvable for the treatment of patients with newly diagnosed multiple myeloma. Before this application may be approved, you must submit complete results and supporting data from the patients enrolled in E1A00, a large randomized Eastern Cooperative Oncology Group (ECOG) study. This information is necessary to demonstrate that thalidomide is safe and effective as treatment for patients with newly diagnosed multiple myeloma. As stated in your submission dated November 1, 2005, you are awaiting additional information from investigators in response to Agency queries. However, because the Agency queries concern response data, the application cannot be approved at this time.

In addition, in December 2003 you submitted data and study reports to support accelerated approval of an indication in patients with relapsed multiple myeloma. To qualify for accelerated approval, your application must demonstrate that Thalidomid is an improvement over existing therapy. Your submission consisted of three single-arm studies in patients with multiple myeloma who had a mean of two prior therapies. Since your submission, Velcade received approval for the treatment of patients with relapsed multiple myeloma who had received 1 or more prior therapies. None of the patients with relapsed multiple myeloma in your submitted application had been treated with Velcade; thus accelerated approval cannot be granted for patients ——————————.

Lastly, since submission of the previous labeling, the frequency of reporting of deep venous thrombosis and pulmonary embolism (DVT/PE) with thalidomide combination therapy has increased. The E1A00 study was prospectively designed to assess the frequency of selected adverse events

between treatment arms. E1A00 study results show a statistically significant difference between treatment arms for DVT/PE (thalidomide/dexamethasone-22.5% compared with dexamethasone alone-4.9%, p=0.002). Therefore, we request that you revise the product labeling for Thalidomid to include this information on DVT/PE.

In addition, it will be necessary for you to submit draft labeling revised as follows:

1. Remove all references to the single-arm studies in patients whose multiple myeloma had relapsed (MAYO-98-80-13 and THAL-MM-99-002).

2. The Thalomid label should be modified to include data on venous thrombotic events (VTEs). We propose using the following language and placing this bolded language in a "black box" for emphasis:

   The use of Thalomid in multiple myeloma has been associated with an increased risk of venous thromboembolic events, such as deep venous thrombosis and pulmonary embolus. This risk increases significantly when thalidomide is used for this indication in combination with standard chemotherapeutic agents including dexamethasone. In one controlled trial the rate of venous thromboembolic events was 22.5% in patients receiving thalidomide in combination with dexamethasone compared to 4.9% in patients receiving dexamethasone alone. Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling.

3. The Warnings section of the label should be strengthened with a bolded warning describing the thromboembolic events risk.

4. A "Dear Health Care Professional" letter should be distributed, notifying prescribers of this information.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level. Additional issues include:

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.

- Include tables that compare frequencies of adverse events in the original NDA with the re-tabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a re-tabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

In addition, as required by 21 CFR 314.550, submit three copies of all promotional materials including promotional labeling and advertisements that you intend to use within 120 days following approval of this product. Submit all proposed materials in draft or mock up form, not final print. Send one copy to The Division of Drug Oncology Products and two copies of both the promotional materials and the proposed package insert directly to:

Division of Drug Marketing, Advertising
and Communications
Food and Drug Administration
5901-B Ammendale Road
Ammendale, Maryland 20705

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed for multiple myeloma until you have been notified in writing that the application is approved.

If you have any questions, call Carl Huntley, Regulatory Project Manager, at (301) 796-1372.

Sincerely,
{See appended electronic signature page}

Robert L. Justice, M.D.
Acting Division Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Justice
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-430

Celgene Corporation
7 Powder Horn Drive
Warren, NJ 07059

ATTN: Megan Parsi
Director, Regulatory Affairs

Dear Ms. Parsi:

Please refer to your new drug application (NDA) dated December 22, 2003, received December 23, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Thalomid (thalidomide) Capsules, 50 mg, 100 mg, and 200 mg.

We acknowledge receipt of your submission dated February 18 and 19, March 29 and 31, April 19 and 23, May 28, June 30, September 13, 24, and 28, 2004.

We have completed our review of this application, as amended, and it is approvable. As we discuss below, you have not yet provided substantial evidence of the effectiveness of Thalomid. Prior to the approval of the application, you must submit results and supporting data to demonstrate that thalidomide is safe and effective as a treatment for patients with multiple myeloma. We believe sufficient support for an accelerated approval could be provided by the results of study E1A100, a large randomized Eastern Oncology Cooperative Group (ECOG) study comparing thalidomide plus dexamethasone to dexamethasone alone in previously untreated multiple myeloma patients. The submission should be complete with full study report and appropriate case report forms. If the trial supports accelerated approval, the ongoing study, Thal-MM-003, could support full approval.

It will be necessary for you to submit draft labeling revised as follows:

- Delete all data and reference to UARK 98-003.
- Incorporate data from E1A00 or Thal-MM-003, or both.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

The application is inadequate for the following reasons:

Deficiencies

Your application failed to provide substantial evidence of effectiveness. Three single arm studies were submitted (MAYO-98-80-13, THAL-MM-99-002, UARK-98-003), and FDA identified problems with each study as outlined below.

The FDA could not rely upon results of the largest study, the 146-patient University of Arkansas study (UARK 98-003). The sponsor or investigator did not follow requisite Federal regulations designed to assure data integrity. Among the deficiencies noted were failure to provide investigators and the Institutional Review Board with major amendments to the protocol, failure to meet the sponsor's general responsibilities, and failure to maintain adequate record keeping. Because of these deficiencies, critical data are either missing or insufficiently recorded and/or validated.

The remaining data in the application are from 62 patients enrolled in the other two studies. The confirmed response rate in the 62 patients in the two evaluable studies was only 13%, and there were no complete responses. The response rate is substantially lower than that claimed in your initial application package and represents only 8 confirmed responses. This contrasts with literature rates of 28% to 48% in similar populations, leaving uncertainty as to the actual effect of the drug. Only one study provided case report forms that could be evaluated for quality and reporting completeness.

Additionally, there were unresolved problems regarding our 74 day filing letter including discrepancies between the E-mail and hard copy responses.

Safety information concerning thalidomide use cannot be extrapolated from the erythema nodosum leprosum (ENL) safety database to the multiple myeloma population because the thalidomide dose used for ENL treatment is lower than that used for multiple myeloma treatment.

In addition, we have the following recommendations and comments:

Recommendations

1. Characterize the reversibility of thalidomide-induced neuropathy.

2. 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 determining 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 thalidomide metabolism. If no other enzymes are detected, a hepatic impairment study is not necessary.

- Activity of metabolites:
  We recommend that you identify thalidomide's major metabolites in urine of multiple myeloma patients. You should screen *in vitro* these metabolites for pharmacological activity. If metabolites are active, you should plan to evaluate their pharmacokinetics. If no active metabolites are identified in the urine, a renal impairment study will not be required.

3. 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.

4. Pharmacokinetics in multiple myeloma patients:
   The bioequivalence simulation approach does not demonstrate bioequivalence between the capsule (Celgene) and the tablet (Chemie Grunenthal) formulations. Pharmacokinetics in multiple myeloma patients treated with the capsule remains unclear. We recommend that you examine thalidomide's 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 both toxicity and effectiveness.

Comments:

1. The half life of thalidomide is 6 hours, and the regimens studied were based on daily dosing. The drug is eliminated prior to the next dose. Effectiveness might be improved by using alternate dosing schedules. Please provide any additional information that would clarify whether alternate dosing regimens have been evaluated or are planned to be evaluated.

2. Consider the impact of drug loss that might occur if dialysis occurs in the absorptive phase following a thalidomide dose. Please consider delaying dialysis for at least 4 hours post dose.

3. The articles you submitted do not adequately support your conclusion that thalidomide has

   If you choose to pursue this mechanism of action in product labeling, you will need to submit additional information to support your conclusions.

4. We note your inclusion of rodent carcinogenicity study results in the proposed product label for thalidomide in the MM indication. A final determination regarding study conclusions and the suitability of the study findings for inclusion in future product labeling will be forthcoming.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level. Additional issues include:

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

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   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

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In addition, as required by 21 CFR 314.550, submit three copies of all promotional materials including promotional labeling and advertisements that you intend to use within 120 days following approval of this product. Submit all proposed materials in draft or mock up form, not final print. Send one copy to the Division of Oncology Drug Products and two copies of both the promotional materials and the proposed package insert directly to:

Division of Drug Marketing, Advertising
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville MD 20857

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed for multiple myeloma until you have been notified in writing that the application is approved.

If you have any questions, call Maureen Pelosi, Regulatory Project Manager, at (301) 594-5778

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Richard Pazdur
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