DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

April 21, 2000

John W. Jackson
CEO
Celgene Corporation
7 Powder Horn Drive
Warren NJ 07059

Re: NDA 20-785
Thalomid (thalidomide) Capsules
MACMIS # 8909

WARNING LETTER

Dear Mr. Jackson:

This Warning Letter concerns Celgene Corporation's ("Celgene's") promotional activities for the marketing of Thalomid (thalidomide) Capsules. The activities were reviewed by the Division of Drug Marketing, Advertising, and Communications ("DDMAC") as part of its monitoring and surveillance program. We have concluded that Celgene has promoted Thalomid (thalidomide) Capsules for unapproved uses in violation of the Federal Food, Drug, and Cosmetic Act (the "Act") and applicable regulations. See 21 U. S. C. §§ 331(a),(b),(d), 352(f),(n), 355(a).

Celgene's actions are particularly troublesome because the July 16, 1998, approval letter for Thalomid specifically notified you that "statements or implications by you that this product may indeed be safe and efficacious in the treatment of diseases or patient populations beyond that approved in your application may be considered a violation of the promotional provisions of the Act." Moreover, the Food and Drug Administration ("FDA") has previously advised Celgene that its promotional activities relating to thalidomide violate the Act. Nonetheless, it is evident that Celgene's violative conduct is continuing.

Background

History of Thalidomide's Approval

Although thalidomide was approved in Europe in 1957, it was not approved by the FDA for use in the United States because of concerns about neuropathy associated with the use of the drug. When the link between thalidomide use and the epidemic of congenital malformations occurring in Europe was recognized, the drug was withdrawn from marketing throughout the world.

On December 20, 1996, Celgene submitted a new drug application ("NDA") under section 505(b)(2) of the Act for Thalomid (thalidomide) capsules. The NDA was approved only for the use of thalidomide in the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum ("ENL") and as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrences. Thalomid (thalidomide) is not approved as monotherapy for such ENL treatment in the presence of moderate to severe neuritis. The approved product labeling for Thalomid does not contain any other indication.

Thalomid was approved under the restricted distribution provisions of 21 C.F.R. § 314.520 ("Subpart H"). Perhaps more than for any other available drug, the need to provide and distribute thalidomide responsibly is essential to the public health.

Subpart H (21 C.F.R. § 314.550) requires the submission of **all** promotional materials, including promotional labeling and advertisements, at least thirty days before the intended time of initial dissemination of the promotional labeling or initial publication of the advertisement. Written, printed, or graphic materials containing product information and disseminated by, or on behalf of, a product manufacturer are generally viewed as promotional labeling.

Prior Communications between FDA and Celgene Regarding Promotion of Thalidomide.

In its July 16, 1998, approval letter to Celgene regarding Thalomid (thalidomide) Capsules, FDA specifically stated that any "statements or implications by you that this product may indeed be safe and efficacious in the treatment of diseases or patient populations beyond that approved in your application may be considered a violation of the promotional provisions of the Act."

Subsequently, on July 30, 1998, DDMAC personnel called Celgene to discuss our concerns about promotional materials containing uses of thalidomide other than those

cited in the FDA approval letter. DDMAC reminded Celgene that its approval letter specifically references the topic of off-label promotion of Thalomid.

On November 9, 1998, DDMAC issued an untitled letter to Celgene regarding the company's issuance of three press releases regarding thalidomide. Those press releases were misleading (lacked fair balance) in that they presented little or no risk information. Moreover, none of the releases had been submitted to FDA as required by Subpart H.

In a December 22, 1998, meeting with Celgene regarding the November 1998 untitled letter, among other issues, FDA expressed strong concern regarding Celgene's promotion of unapproved uses of thalidomide, and its failure to fully state risks, particularly in light of "severe risks" associated with use of the product.

Promotion of Unapproved Uses

Celgene has engaged in promotional activities that state or suggest that Thalomid is safe and effective for use in treating multiple myeloma. Celgene has also represented to physicians that Thalomid can be used to treat various cancers, for cancer patient "weight loss," and to promote a feeling of "general well-being" in these same patients.

This past fall, a Celgene sales representative in the Chicago area promoted the use of thalidomide in patients with cancer, particularly multiple myeloma, to a physician. As part of the sales presentation, the Celgene representative stated to the physician, "wouldn't you consider using thalidomide in a patient with myeloma who did not achieve an adequate response with other agents, because of thalidomide's anti-angiogenesis potential?" In this promotional context, the representative also handed to the physician a copy of a press release issued by the Arkansas Cancer Research Center Foundation on September 28, 1998, entitled, *Thalidomide Shows Promising Results in Patients with Multiple Myeloma*. This document refers to initial findings in myeloma patients as "extraordinary – especially when one considers that these patients had failed all other therapy." Celgene has also utilized other third-party press releases to promote thalidomide for use in treating multiple myeloma.

More recently, another Celgene sales representative in the northeastern United States promoted the use of thalidomide in cancer patients to an oncologist by stating that thalidomide is "good for weight loss," that it could be used "as an appetite stimulant," and that it is a "great drug for feelings of general well-being." When the oncologist asked the sales representative if thalidomide had FDA approval for these indications, the sales representative stated, "no, but do you want some material anyway?" This

sales presentation was delivered during a luncheon provided by Celgene for an oncology practice group.

These actions constitute violations of the Act and applicable regulations.

Furthermore, we have a report that Celgene has stated publicly during an investors' meeting that Celgene sales representatives would be promoting thalidomide for off-label uses in "detail" sessions with physicians. Statements of this type are evidence that Celgene intends the promotion and sale of thalidomide for unapproved uses in violation of the Act.

Finally, DDMAC is concerned that Celgene is failing to comply with the regulations under which its drug, Thalomid, was approved. Promotional activities for Thalomid are subject to 21 C.F.R. § 314.550 because Thalomid is subject to restricted distribution provisions. Section 314.550 requires the submission of all promotional materials, including promotional labeling and advertisements, at least thirty days before the intended time of initial dissemination of the promotional labeling or initial publication of the advertisement.

Conclusions and Requested Actions

Celgene is demonstrating a continuing pattern and practice of violative behavior that evince its failure to comply with the conditions under which Thalomid was approved. Previous discussions with Celgene have not resulted in Celgene's compliance with the Act. We therefore ask that you provide a detailed response to the issues raised in this Warning Letter – specifically that Celgene is promoting Thalomid for unapproved uses. This response should contain an action plan that includes:

1. Immediately ceasing promotional activities containing the same or similar violations as described in this letter.

2. Assurance to FDA that Celgene is not promoting Thalomid for unapproved uses anywhere in the United States or its territories and possessions.

3. Within fifteen calendar days of the date of this letter, dissemination of a copy of this Warning Letter to all of your managers and representatives.

4. Submitting in writing, a proposed corrective action. This corrective action may be determined through discussions between Celgene and DDMAC.

5. Submitting in writing, Celgene's intent to comply with these requested actions (numbers 1 through 4 above).

The violations discussed in this letter do not necessarily constitute an exhaustive list. We are continuing to evaluate other aspects of Celgene's promotional campaign for Thalomid and we may determine that additional remedial measures will be necessary to fully correct the false or misleading messages resulting from Celgene's violative conduct.

Celgene should respond to this letter no later than May 5, 2000. If Celgene has any questions or comments, please contact Lesley Frank, Ph.D., J.D., or Mark Askine, R.Ph. by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds Celgene that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID # 8909.

Failure to respond to this letter may result in regulatory action, including seizure and/or injunction, without further notice.

Sincerely,

/S/

Thomas W. Abrams, R.Ph., M.B.A.
Director
Division of Drug Marketing,
Advertising, and Communications