THE UNITED STATES DEPARTMENT OF
HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

05 MAY -4 A9:29

Petition to Require Celgene Corporation to Revise the Labeling of Thalomid® Capsules to Strengthen Warnings of the Potential for Serious Adverse Events When Prescribed in Combination with other Cancer Treatment Therapies	}	**Docket No.** _____

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State of Connecticut

May 4, 2005

2005P-0167

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CITIZEN PETITION

Richard Blumenthal, the Attorney General for the State of Connecticut ("Petitioner"), submits this Petition to request action by the Food and Drug Administration ("FDA") regarding Celgene Corporation's ("Celgene") Thalomid® Capsules ("Thalomid"), which is currently approved, under extremely strict regulation[1], in the United States solely for the treatment of moderate to severe *erythema nodosum leprosum* ("ENL"), an inflammatory condition found in some patients with Hansen's disease, otherwise more commonly known as leprosy. As would be expected given that it is approved only for a condition that afflicts a very small number of Americans, the vast majority of all prescriptions written for Thalomid are for off-label uses. Indeed, Celgene representatives have publicly acknowledged that approximately ninety-two percent (92%) of all prescriptions written for the drug are for the off-label treatment of cancers, primarily multiple myeloma and other hematological (blood) cancers.[2] Thus, Thalomid is a leprosy drug in name only -- by any realistic measure it is in fact a cancer drug.[3]

As the FDA has rightly recognized, there is nothing inherently wrong with healthcare professionals prescribing -- or patients using -- drugs for off-label uses and such use can lead to important treatment breakthroughs.[4] Indeed, Thalomid is an example of such a breakthrough: by all indications, it provides a valuable treatment option for patients stricken by certain forms of cancer. This petition in no way seeks to limit Thalomid's use for the treatment of cancer, or any

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[1] As will be discussed in detail below, this strict regulation is necessary due to the severe birth defects that can result from fetal exposure to thalidomide.

[2] *See, e.g.*, Comments of Bob Hugin, CFO, Celgene Corp., at the Lehman Bros. Global Health Care Conf., p. 3 (Mar. 31, 2005) (stating that about 92% of Thalomid prescriptions are for cancer).

[3] Celgene's 2003 Annual Report illustrates this point well. The only words on its cover aside from "Celgene 2003" is the phrase "[b]ecause there are more than 23,000,000 patients suffering from cancer worldwide." The Annual Report then goes on to focus extensively on Thalomid's use to treat cancer. It mentions ENL and leprosy only in passing, well into the 70-page report.

[4] Of course, that is a wholly distinct issue from drug manufacturers marketing drugs for off-label uses, a practice that poses significant concerns by, *inter alia*, allowing companies to avoid the approval system designed to ensure drug safety.

other condition for which the prescribing healthcare professional believes, based on his or her professional judgment and complete information, it is the best available treatment.

What this petition does seek to do is to provide healthcare professionals and patients with sufficient access to all the information necessary to make the best treatment decision possible. As the petition will discuss in detail, there are significant safety concerns for patients whose cancer is being treated with Thalomid that are not fully addressed in the drug's labeling and, consequently, of which healthcare professionals may not be aware. Specifically, a comprehensive review of clinical data by the Research on Adverse Drug events And Reports ("RADAR") project[5] indicates that the off-label use of Thalomid for the treatment of multiple myeloma and other blood-related cancers, particularly when used in combination with certain other cancer-treating therapies, raises a significant potential for severe and in some cases life-threatening or fatal blood clots developing in patients treated with such regimens.[6]

Thalomid's current labeling does not adequately reflect these serious concerns, which both Celgene and its overseas business partner recognize exist.[7] Nor does Thalomid's current labeling advise healthcare professionals and patients of specific prophylactic measures that may lessen the possibility of such occurrences. The RADAR project's analysis makes clear that the

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[5] The RADAR project is a National Cancer Institute ("NCI") funded collaboration of hematologists/oncologists, clinical pharmacologists, pharmacists, and statisticians affiliated with The Robert H. Lurie Comprehensive Cancer Center of Northwestern University—an NCI-designated comprehensive cancer center. The program is designed to identify and report potentially fatal adverse drug reactions with a particular emphasis on toxicities that occur in the hematology/oncology setting. The attached RADAR report is a draft and may be subject to some changes before final publication.

[6] Although it is difficult to know exactly how many cancer patients, in Connecticut and nationwide, treated with Thalomid suffer such adverse events, the petitioner has specifically been informed of one such incident in Connecticut that resulted in heart failure and was nearly fatal to the patient.

[7] As will be discussed in detail below, Celgene's website contains additional language not included in its labeling or the Physician's Desk Reference indicating that patients being treated with thalidomide in conjunction with other unspecified agents may have an increased risk of blood clots. Even aside from its being available only on the web, that language is plainly insufficient to adequately warn patients and providers of the dangers posed. By contrast, as is also discussed in detail below, Celgene's overseas business partner, Pharmion Corporation, includes in its labeling detailed information as to the increased risk of blood clots in cancer patients from the combination of Thalomid and specific chemotherapy agents and recommends that the prescriber consider prophylactic measures to avoid such adverse reactions.

lack of such information may endanger the health of patients taking Thalomid, nearly all of whom use it off-label to treat cancer. That danger is particularly acute now given that Thalomid's inclusion as part of the Medicare Replacement Drug Demonstration Project as a treatment for multiple myeloma will likely lead to a significant number of new patients being prescribed the drug -- newly diagnosed patients are the very group most at risk for suffering the Thalomid-related side effects identified by the RADAR project.

Beyond the danger posed by Thalomid's inadequate labeling, there is a real danger that Celgene's business practices will undermine the very strict regulatory framework, designed to prevent birth defects, upon which Thalomid's approval was predicated and upon which Celgene's patent is based. Once Thalomid's potential as an anti-cancer agent began to be established, Celgene began a pattern of constant price increases based on the knowledge that patients will pay whatever they can to beat cancer.[8] As will be discussed in detail below, those price increases impose a significant burden on patients[9] and threaten to drive them overseas and outside the elaborate regulatory framework the FDA required to prevent a repeat of thalidomide's tragic history.

Therefore, the undersigned requests that the Commissioner of the FDA immediately require Celgene to take various actions with respect to the labeling of Thalomid to protect the public's health and safety, including: strengthening the drug's "black box" warning statement,

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[8] *See, e.g.*, Comments of Dr. Alan Lewis, Pres., Celgene San Diego, at the JMP Secs. LLC Research Conf.. pp. 4-5 (Mar. 2, 2005) (noting that when Thalomid was initially approved, it was intended to treat AIDS and Celgene "priced it accordingly"; goes on to state that once evidence showed that Thalomid was "a very effective oncology product," Celgene began "slowly increasing the price of the product to really reflect its value to the patient" and that "there is definitely likely to be a pricing increase this year"); *see also* Comments of John Jackson, CEO, Celgene Corp., at the Smith Barney Citigroup Healthcare Conf., p. 2 (Mar. 30, 2005) (noting that "[p]rescription growth [for Thalomid] has clearly slowed. Fortunately, we're in a position where we've been able to significantly increase price").

[9] One prominent Connecticut oncologist indicated that many of his patients express concern about the price increases for Thalomid and that those increases make it more difficult for his patients to afford the necessary treatment.

supplementing the labeling with additional bolded warnings, conducting a phase IV clinical trial that addresses prospectively the risks and benefits of alternative efforts to limit the risk of blood clots, initiating a "Dear Healthcare Professional" letter notifying prescribers of the increased potential for serious blood clots when Thalomid is used in combination with other therapies, expanding the risk management program implemented by Celgene to ensure the safe use of Thalomid and taking all other actions necessary to protect the integrity of that risk management program.[10]

This petition is submitted pursuant to § 4 (d) of the Administrative Procedure Act, 5 U.S.C. § 553 (e), 21 C.F.R. § 10.30, and pursuant to §§ 331(a) and 352(a) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. §§ 301, *et seq.*

I. BACKGROUND

A. The Development of Thalomid and its Approval to Treat ENL

The long and infamous history of thalidomide is well-documented in the annals of those pharmaceuticals whose latent side effects were discovered only after a significant number of patients were prescribed the drug. In the case of thalidomide, the drug was first marketed as a sedative outside the United States in the 1950s and early 1960s, and was subsequently linked with causing severe birth defects. The teratogenicity[11] of thalidomide is estimated to have caused disabling birth defects in upwards of 10,000 people worldwide, an estimated forty percent (40%) of whom died within a year of birth.[12]

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[10] Again, this petition is in no way intended to limit patients' access to Thalomid for the treatment of cancer or to suggest that the drug should be removed from the Medicare Replacement Drug Demonstration Project or the market as a whole.

[11] Teratogenicity is a side effect of thalidomide and is defined as the production of physical defects in offspring in utero (i.e., causing birth defects).

[12] *See* Pannikar V., *The Return of Thalidomide: New Uses and Renewed Concerns*, World Health Org. Pharmaceuticals Newsletter, 2003, 2:11.

Due initially to the neuropathy it can cause and later to its established teratogenic effects on developing embryos, thalidomide was never approved for use in the United States during the 1950s and 1960s. That changed, however, in 1998, when Celgene received FDA approval to market thalidomide as Thalomid for the treatment of ENL, a condition sometimes associated with leprosy. Leprosy was and continues to be very rare in the United States.[13] Moreover, even in individuals with leprosy "[t]oday ENL reaction is a rare complication . . . [and m]ost of the ENL reactions are mild in nature and do not require any specific treatment."[14] Therefore, the approved market for Thalomid was extremely limited at the time of approval and it remains so today. Indeed, some physicians and organizations have gone so far as to conclude that because other therapies for ENL are safer and more effective, "there is no place for thalidomide in leprosy" treatment.[15]

B. The STEPS Program

Thalomid's status in its already narrowly approved market was further complicated by its severe teratogenicity. To ensure against the possibility of serious fetal deformities caused by the drug, the FDA made Thalomid's approval contingent on Celgene's compliance with what is generally understood to be the most tightly restricted postmarketing drug distribution risk management program of any drug ever approved by the FDA.[16] Known as the System for Thalidomide Education and Prescribing Safety ("STEPS"), the program includes a number of

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[13] *See, e.g.*, Centers for Disease Control Disease Info., *Hansen's Disease (Leprosy)* (noting that leprosy is a nationally notifiable disease in the United States and that "[i]n 2002, 96 cases occurring in the United States were reported to the CDC").

[14] Pannikar V., *The Return of Thalidomide. New Uses and Renewed Concerns*, World Health Org. Pharmaceuticals Newsletter, 2003, 2:11; *see also The News Hour with Jim Lehrer: Return of Thalidomide* (PBS television broadcast, Aug. 4, 1998) (hereinafter "*The News Hour*") (statement by FDA Acting Commissioner Dr. Michael Friedman) (noting that ENL is a "very rare complication of leprosy").

[15] *See Pannikar, supra*; *see also* Pan Am. Health Org., *No Role for Thalidomide in Leprosy* (hard copy attached) (concluding, apparently based on Pannikar paper, that "**Leprosy does not need thalidomide**." (emphasis in original)).

[16] *FDA Talk Paper*, available at: www.fda.gov/bbs/topics/ANSWERS/ANS00887

tools to manage the risks of fetal exposure to thalidomide. In general, only physicians who are registered in the STEPS program can prescribe Thalomid, and those patients receiving the drug, both male and female, must comply with mandatory and ongoing contraceptive measures, patient registration, education, and survey requirements. Further, the drug can only be distributed to, and dispensed by, pharmacies and pharmacists registered in the STEPS program.[17] In public statements surrounding Thalomid's approval, the FDA's Acting Commissioner recognized the "very serious concerns" about the drug's safety but noted the "very intensive [and] . . . very ambitious" program to limit the risk and assured the public that the FDA "will be carefully monitoring how many patients [use the drug], for what diseases, under what circumstances we're going to be watching this very, very closely."[18] The FDA's insistence has paid off, as the STEPS program has been quite successful in limiting birth-defects caused by thalidomide.

C. The Extensive Off-Label Use of Thalomid

Despite Thalomid's narrow indication, questionable usefulness for its approved indication and severe side effects, Celgene has been able to use it as its "financial engine" to make the company profitable -- for the first time in its history -- based almost entirely on off-label prescribing. [19] Although Celgene initially only sought and obtained approval for Thalomid to treat ENL, it anticipated at the time of approval -- and physicians soon confirmed -- that the

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[17] *Id.*

[18] *The News Hour*, *supra* (statement by FDA Acting Commissioner Dr. Michael Friedman).

[19] *See, e.g* , Comments of Robert Hugin, Vice Pres. and CFO, Celgene Corp., at the Lehman Bros. Global Health Care Conf. (Mar. 31, 2005) ("Thalomid is the financial engine, has been for the past . . . number of years. It is approved for narrow indication related to the treatment of leprosy, *erythema nodosum leprosum*. But because of its multiple mechanisms of action, it's explored in a number of important other indications in cancer, primarily."); *Celgene Corp. 2003 Annual Report* at 2 ("Based largely on THALOMID sales, we generated more than $271 million in revenues in 2003, delivered our first full-year positive earnings, and reinvested 45% of our total revenues into accelerated R&D programs."); Comments of John Jackson, CEO, Celgene Corp., at the Smith Barney Citigroup Healthcare Conf., p. 2 (Mar. 30, 2005) (estimating that total 2005 revenues to Celgene from Thalomid would be "in the range of 400 million").

drug was effective off-label in treating various other conditions, such as AIDS wasting[20] and certain malignancies, particularly hematologic cancers.[21]

Of course, using Thalomid to treat patients with AIDS or cancer (or any other condition other than ENL) constitutes an off-label use. Although FDA regulations prohibit a manufacturer from marketing its drug for off-label uses, prescribers are not so constrained. In fact, physicians commonly prescribe drugs for uses not indicated in the drug's package insert, and such uses can lead to the discovery of new, more effective, therapies. Concern arises, however, if there is evidence that the off-label use presents a safety risk to the patient, especially if the manufacturer may have information of such possible adverse consequences from off-label prescribing and fails to adequately warn the healthcare professional community and patients of such risks.

According to the FDA, prescription data reviewed by the agency demonstrates that "almost 90% of the prescribing of Thalomid is for oncologic conditions."[22] (As discussed above, Celgene has placed the number at 92%) Further, that trend is expected to continue as Celgene has sought approval from the FDA to expand its Thalomid indication to treat multiple myeloma. Although the FDA has not approved this supplemental new drug application, the agency did issue an "approvable" letter in October, 2004, and the company expects to receive final approval sometime in the second half of 2005.[23] In addition, regardless of whether or when Celgene receives FDA approval for this expanded indication, the trend of off-label prescribing is likely to continue, as Thalomid is one of the drugs for which Medicare patients undergoing treatment for multiple myeloma will receive partial reimbursement from the federal government under the

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[20] AIDS wasting is generally defined as profound involuntary weight loss of greater than 10% of baseline body weight plus either chronic diarrhea or chronic weakness and documented fever.

[21] Thalomid, or thalidomide, falls within a class of drugs known as immunomodulatory drugs, or IMiDs. IMiDs appear to inhibit both the growth and survival of myeloma cells as well as the growth of new blood vessels that feed tumors.

[22] *See* Memorandum from Carl Kraus, M.D., Medical Officer, Division of Special Pathogen and Immunologic Drug Products, FDA, January 29, 2004.

[23] *See* Celgene Corp Form 10-K/A, p. 35 (Filed March 21, 2005).

Medicare Replacement Drug Demonstration Project.[24] The inclusion of Thalomid in the project for multiple myeloma may be viewed by healthcare providers as an implicit approval by the federal government that the drug is efficacious and safe for this specific off-label use and that all safety concerns related to that use are properly identified in the drug's labeling.[25]

D. Safety Concerns Relating to the Off-Label Use of Thalomid to Treat Cancer

When Thalomid is used for its approved indication, the most common and serious toxicity -- aside from its teratogenicity -- is neuropathy.[26] When Thalomid is used off-label to treat cancer, however, a wealth of evidence indicates that there is a significantly increased risk of other serious -- and potentially fatal -- side effects. Specifically, the RADAR project conducted a comprehensive review of all adverse drug event reports contained in FDA databases and medical literature relating to the use of thalidomide to treat cancer. That review -- of 39 clinical trials involving 1,784 patients -- indicated that there is a significant increase in the risk of potentially fatal deep venous thrombosis ("DVT") and pulmonary embolism ("PE") occurring in cancer patients treated with Thalomid.

Moreover, the potential for developing a DVT or PE is markedly increased when Thalomid is used in combination with certain other cancer-treating therapies, such as doxorubicin. For instance, as will be discussed in more detail in Section III, below, when Thalomid was used as a single-therapy, the incidence of a patient developing a DVT or PE was

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[24] The Medicare Replacement Drug Demonstration, was mandated under Section 641 of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 ("MMA"). As set by Congress, enrollment in the demonstration will be open to 50,000 people and total spending on the covered drugs will be up to $500 million. Under this initiative, Medicare will pay for certain drugs and biologicals that can be taken by the patient at home and that replace drugs which are currently covered under Medicare Part B when given in a doctor's office. In addition, newer, more effective medications that replace some currently covered oral anti-cancer drugs will also be covered.

[25] The Centers for Medicare and Medicaid Services established an inter-agency panel of clinicians to determine criteria used to identify and ultimately select drugs used for the project.

[26] *See, e.g.*, V. Chaudhry, MD *et al.*, *Thalidomide-Induced Neuropathy*, *Neurology* 59:1872 (2002). Neuropathy is a form of nerve damage that often causes sensations of burning, freezing, throbbing and/or shooting pain.

5%. When Thalomid was combined with concomitant corticosteroid therapy,[27] the potential for a DVT or PE increased to 13%. This likelihood of encountering a DVT or PE rose to 17% for those patients treated with Thalomid and a chemotherapy agent. But even these statistics do not present the entire risk picture, as the RADAR study found that patients with multiple myeloma treated with Thalomid and doxorubicin stood an almost 33% risk of forming a DVT or PE.

Yet while DVT/PE represents the greatest risk of adverse events to cancer patients undergoing concomitant Thalomid and chemotherapy treatment, and despite Celgene's admission that the drug today is prescribed virtually exclusively for cancer treatment, Thalomid's labeling still does not adequately warn healthcare professionals of the drug's potential for causing these serious adverse events. In fact, the current package insert warnings related to "Thrombotic Events", which were last updated by the company in October, 2003, provide that patients treated with Thalomid "*may* have an increased incidence" of DVT or PE. (emphasis added). Further, notwithstanding the research conducted by numerous clinical trials and compiled through the RADAR report, the warning is equivocal -- at best -- in identifying any link between combination Thalomid and chemotherapy treatment and the incidence of DVT/PE and states "*[i]t is not known if concomitant therapy with other medications, including anticancer agents, are a contributing factor.*" (emphasis added).

Not only is Thalomid's labeling deficient in expressly warning prescribers of the serious potential for side effects posed when the drug is used concomitantly with chemotherapy agents, but the labeling also fails to provide prescribers with prophylactic measures that can be initiated

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[27] Corticosteroids are used to provide relief for inflamed areas of the body. They lessen swelling, redness, itching, and allergic reactions. They are often used for a number of other diseases such as asthma, auto immune diseases, lymphomas and other blood cancers. When used in combination with chemotherapy, corticosteroids may enhance the killing of lymphoma cells, and also help mitigate (reduce) fatigue, nausea, and loss of appetite associated with chemotherapy.

to further lessen the potential for DVT or PE. As noted in the RADAR report, several studies reviewed by the report's authors observed that there were marked decreases in study patients experiencing a DVT or PE when their combination Thalomid and chemotherapy treatment regimen included administration of blood thinners such as coumadin or low molecular weight heparin.

II. ACTION REQUESTED

By all accounts, the majority of Thalomid prescriptions are written off-label to treat various cancers, and the majority of those prescriptions are written for multiple myeloma.[28] 21 C.F.R. § 201.57 requires drug manufacturers to include certain information in their labeling, including warnings, precautions and the identification of adverse reactions associated with the use of the drug.[29] The Federal Food, Drug and Cosmetic Act provides that a drug shall be deemed to be "misbranded" if its labeling is "false or misleading in any particular." 21 U.S.C. § 352 (a); *see also* 21 U.S.C. § 321(n). Given that a vast number of Thalomid prescriptions are prescribed off-label as part of a cancer patient's treatment regimen, and pursuant to 21 C.F.R. § 201.57 and 21 U.S.C. § 352 (a), the Petitioner requests that the Commissioner act immediately to require Celgene to inform all prescribers of the risks associated with prescribing Thalomid concomitant with chemotherapy agents. Such immediate action, as requested below, must include the dissemination of specific warning information to healthcare professionals related to prescribing Thalomid and the revision of the current safety labeling of Thalomid, including:

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[28] Comments of Bob Hugin, CFO, Celgene Corp., at the Lehman Bros. Global Health Care Conf., p. 3 (Mar. 31, 2005) (stating that about 92% of Thalomid prescriptions are for cancer and about 80% are for myeloma).

[29] A prescription drug's "labeling" includes "all written, printed or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce." 21 C.F.R. § 1.3.

A. Revising the Black Box Label

The following warning should be required to be added to the labeling of Thalomid:

> **WARNING:** (The following is in addition to the warnings currently contained in the labeling)
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> **In malignant conditions, such as multiple myeloma, patients are predisposed to a hypercoagulable state. Thus, caution should be used when Thalomid is combined with chemotherapy, as venous thromboembolism is a potential complication. An unexpectedly high risk of venous thromboembolism has been observed when Thalomid is combined with chemotherapy for newly diagnosed patients with myeloma. The potential for experiencing thrombotic events is particularly acute when Thalomid is used concomitant with vincristine, doxorubicin and dexamethasone.**

B. Strengthened Warning and Safety Labeling

In malignant conditions, patients are predisposed to a hypercoagulable state. As a result, the risk of thromboembolism is heightened due to the potential for activated protein C resistance or elevated levels of Factor VIII and von Willebrand factor. Caution should be used when Thalomid is combined with chemotherapy, as a marked increase in the number of patients experiencing a thrombotic event have been reported. An unexpectedly high risk of venous thromboembolism has been observed when Thalomid is combined with chemotherapy for newly diagnosed patients with myeloma. The potential for experiencing thrombotic events is particularly acute when Thalomid is used concomitant with vincristine, doxorubicin or dexamethasone.

It is recommended that when Thalomid is used concomitant with chemotherapy agents, prescribers should consider the use of prophylactic anticoagulation treatments such as warfarin, coumadin or low molecular weight heparin. Such treatments are reported to have decreased the rate of thromboembolic complications. This information should be added to relevant sections of

the labeling, including but not limited to, the following sections: Warnings (Thrombotic Events), Adverse Reactions, Other Adverse Events Observed in Cancer Patients (Proposed New Section)[30], Other Adverse Events in the Published Literature or Reported from Other Sources. In addition, adverse reactions associated with thrombotic events identified and reported during post-approval use of Thalomid should be included in a Post-Marketing Experience section added to the drug's labeling.

C. Phase IV Study to Determine Most Effective Prophylaxis for Thalomid-Related DVT/PE

To follow-up on the reference to prophylactic anticoagulation treatments requested in the strengthened warning and safety labeling, Celgene should be required to complete a phase IV safety study among persons with multiple myeloma who receive thalidomide and doxorubicin or corticosteriods. The two major objectives would be: 1) to assess the safety and efficacy of alternative thromboembolism prophylaxis regimens, including prophylactic dosages of low molecular weight heparin versus coumadin administered at 1 milligram or 3 milligrams per day; and 2) to assess the safety and efficacy of reinitiating thalidomide-containing chemotherapy or corticosteroid regimens among cancer patients who develop a thromboembolic complication while receiving thalidomide-containing chemotherapy or corticosteroid regimens. Once that study is completed, its findings should be made a part of Thalomid's labeling to ensure that healthcare professionals are aware of the best method to prevent thromboembolic complications.[31]

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[30] The labeling currently contains a section devoted to "Other Adverse Events Observed in ENL Patients." As discussed above, ENL patients constitute only a fraction of the patients being treated with Thalomid.

[31] The doctors with whom the petitioner has discussed issues relating to DVT/PE resulting from treatment with Thalomid believe that the requested study is particularly important because the existing medical literature does not provide a clear recommendation as to which prophylaxis works best for cancer patients under the circumstances.

D. The Issuance of a "Dear Healthcare Professional" Letter

Celgene should be required immediately to inform all prescribers of Thalomid in the United States about the thrombotic risks prevalent when prescribing Thalomid in combination with other chemotherapy agents. Further, Celgene should disseminate information recommending that cancer patients, as well as other patients with increased plasma viscosity, should be considered for appropriate prophylaxis such as coumadin or low molecular weight heparin.

E. The Expansion of the STEPS Program to Lessen the Risk of the Incidence of Thrombotic Events.

The heightened potential for the development of a serious or life threatening DVT/PE when a patient is prescribed Thalomid concomitant with chemotherapy agents warrants the expansion of the risk management goals for Thalomid to include the prevention or mitigation of DVT/PE. Additional elements added to the STEPS program should include, but not be limited to, the following:

- The addition of a 7th risk group identified as cancer patients treated concomitantly with Thalomid and a chemotherapy agent. This category can be further subdivided to include (i) previously untreated patients (defined as those patients receiving Thalomid as part of the initial chemotherapy regimen for cancer), (ii) patients prescribed Thalomid in combination withdoxorubicin, erythropoietic agents, gemcitabine, or corticosteroids;
- The expansion of the Interactive Voice Response System survey to include the receipt of information relevant to identify the risk factors for DVT/PE;
- Mandatory reporting of any DVT/PE to Celgene and the FDA.

F. All Other Actions Necessary to Protect the Integrity of the STEPS Program

At the time the FDA approved Thalomid for treatment of ENL, many people -- including many whose lives were impacted by thalidomide-associated birth defects -- justifiably raised concerns that Thalomid's approval would usher in a new generation of infants deformed by the drug. The FDA assured the public that it would be vigilant and that the STEPS program could and would protect against such tragedies. To the FDA's credit, the program has been remarkably successful in preventing such birth defects. However, that success may now be jeopardized by Celgene's business strategy of continually raising prices for Thalomid. With each price increase, it becomes more difficult for many cancer patients in the United States to afford Thalomid[32] and that increases the likelihood that they will seek to purchase thalidomide overseas (although it may be difficult for them to verify that what they purchased is, in fact, thalidomide rather than a counterfeit version that is unsafe or completely ineffective), and potentially outside the STEPS program. On a basic level, driving a subset of patients outside the STEPS program by continually increasing prices will limit the efficacy of the relief this petition seeks: requiring that the STEPS program include information concerning the increased risk of thromoboembolism. On a much more fundamental level, it raises the grim specter that Americans may obtain the drug without the necessary educational and monitoring safeguards and that their children will suffer.

[32] To Celgene's credit, it provides Thalomid to a number of patients who could not otherwise afford it. Of course, that mitigates, but does not solve, the problems attendant to the company's continuous price increases.

III. REASONS FOR ACTION REQUESTED

Thalomid is perhaps the quintessential exemplar of the issues raised by off-label prescribing. It has an extremely narrow approved indication (for which its usefulness is open to some question)[33] and is almost exclusively used off-label[34] in patients who are suffering from a life-threatening disease. Moreover, and more fundamentally, it has known severe and debilitating side effects which have led the FDA to subject it to stricter regulation than perhaps any other drug. Finally, thalidomide is uniquely important as it is the first and only cancer drug included in the Medicare Drug Replacement Demonstration Project whose use is almost entirely off-label. As such, Medicare recipients who participate in the Demonstration Project are not fully informed about the risks and prophylaxis strategies for thalidomide-associated thromboembolism that occurs in the oncology setting. Viewing all these factors, it is clear that Thalomid represents the confluence of all the problems and promise that make the proper regulation of off-label prescribing such an important issue.

The question thus becomes how to address those problems and unlock the promise of scientific progress while still protecting patients who are understandably eager to find a cure for their cancer. The FDA's approach, apparently, has been to ignore the issue. It has treated Thalomid as nothing more than a leprosy drug, remaining willfully blind to the fact -- well known to both the agency and Thalomid's manufacturer -- that upwards of ninety percent of the drug's prescriptions are to treat cancer. This case painfully demonstrates why ignoring reality is not a viable approach. It has left the vast majority of patients being treated with Thalomid, and

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[33] *See, e.g.*, Pannıkar V., *The Return of Thalidomide: New Uses and Renewed Concerns*, World Health Org. Pharmaceuticals Newsletter, 2003, 2:11

[34] *See, e.g.*, Memorandum from Carl Kraus, M.D., Medical Officer, Division of Special Pathogen and Immunologic Drug Products, FDA, January 29, 2004 (noting that approximately 90% of Thalomid's usage is for oncologic conditions); Comments of Robert Hugin, Vice Pres. and CFO, Celgene Corp., at the Lehman Bros. Global Health Care Conf. (Mar. 31, 2005) (stating that 92% of Thalomid's prescriptions are for cancer treatment).

many of their healthcare providers, without critical information about the significant safety issues raised by the use of Thalomid to treat cancer. This petition asks the FDA to correct that unfortunate course of conduct, and provide healthcare providers and patients with all the information they need to ensure treatment decisions are based on the most informed and reliable medical information.

A. The Off-Label Use of Thalomid Raises Significant Safety Concerns Not Adequately Disclosed in its Labeling

When Thalomid is used for its approved indication, the most common and serious toxicity -- aside from its teratogenicity -- is neuropathy.[35] When Thalomid is used off-label to treat cancer, however, a wealth of evidence indicates that there is a significantly increased risk of other serious, and potentially fatal, side effects. Specifically, a comprehensive review by the RADAR project of all adverse event reports contained in FDA databases and medical literature relating to the use of thalidomide to treat cancer -- encompassing 39 phase II and phase III oncology trials involving 1,784 patients -- indicated that there is a significant increase in the risk of DVT or PE in cancer patients treated with thalidomide. That increased risk associated with off-label use -- which, as discussed above, constitutes nearly the entire United States' market for Thalomid -- raises serious safety concerns that are not properly addressed in Thalomid's current labeling and of which healthcare professionals and patients may not be aware.

The RADAR project's review of existing clinical data makes clear the increased risk. Two studies in particular show its potential magnitude. In 2001, reports from one phase II and one phase III clinical trial identified rates of 28% and 43%, respectively, for the development of DVT and PE when thalidomide-containing chemotherapy regimens were administered to cancer

[35] *See, e.g.*, V. Chaudhry, MD *et al.*, *Thalidomide-Induced Neuropathy*, *Neurology* 59:1872 (2002). Neuropathy is a form of nerve damage that often causes sensations of burning, freezing, throbbing and/or shooting pain.

patients.[36] The latter study, which closely compared combination chemotherapy regimens with and without thalidomide, showed a fourteen-fold increase (3% versus 43%) in thromboembolic complications in patients whose regimens included thalidomide.

Although the increase found in that study was high relative to other studies and the incidence rate in the studies as a whole varied based on certain variables (including diagnosis, stage of treatment, concurrent therapies and concomitant use of prophylaxis against thromboembolism), the overall data leaves little question that there was an increased risk of DVT and PE in cancer patients treated with Thalomid. Over the entirety of the clinical trials the RADAR project surveyed, among multiple myeloma patients treated with thalidomide without DVT prophylaxis, thromboembolism rates ranged from a low of one in 20 with thalidomide alone to a high of about one in three individuals treated with concomitant doxorubicin. Furthermore, while the median number of days before the occurrence of a thalidomide-associated DVT/PE was 52 days, 5% of the cases reported a thrombotic event within two weeks of the initiation of thalidomide treatment.

All in all, while thalidomide-associated DVT/PE was reported for persons with all types of cancer, the mean incidence rates of those adverse drug reactions were significantly greater when chemotherapy or corticosteroids were also administered. The RADAR project's analysis indicates that the clear weight of clinical authority raises a serious concern that thalidomide-treated cancer patients have an increased incidence of PE and/or DVT and that concomitant administration of other anticancer agents (including doxorubicin, gemcitabine or corticosteroids)

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[36] *See* Zangari M, Anaissie E, Barlogie B, et al. *Increased risk of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide and chemotherapy*, Blood. 2001; 98:1614-1615; Figg W, Arlen P, Gulley J, et al., *A Randomized Phase II Trial of Docetaxel (Taxotere) Plus Thalidomide in Androgen-Independent Prostate Cancer*, Semin Oncol. 2001(August); 28(suppl):62-66.

is associated with a marked increase in the rates of thalidomide-associated venous thromboembolism.

Thalomid's labeling does not reflect those serious concerns relating to the concomitant administration of thalidomide and other anticancer agents. To the contrary, the current labeling specifically gives the impression that such concerns are not validly supported. In its section dedicated to thrombotic events, it states that

> Thrombotic events have been reported in patients treated with THALOMID® (thalidomide). Patients with neoplastic and various inflammatory conditions being treated with THALOMID® (thalidomide) *may* have an increased incidence of pulmonary embolism, deep vein thrombophlebitis, or thrombosis. *It is not known if concomitant therapy with other medications, including anticancer agents, are a contributing factor.*

(emphasis added). Far from alerting prescribers and patients to the likelihood that concomitant treatment with thalidomide and other anticancer agents increases the risk of thrombotic events, as the RADAR project's analysis and the studies upon which it is based indicate, the "it is not known"[37] language (proposed by Celgene two years after the first reports of thromboembolic events) actually gives the impression that such issues either have not been examined or have been examined but the evidence has been found lacking.

Even more harmful, the labeling does nothing to inform healthcare professionals and patients of the specific risks that are raised by certain combinations of therapies, most notably thalidomide and doxorubicin, which the RADAR project concluded resulted in an approximately one in three chance of a thromboembolism. Moreover, by indicating that there is no evidence showing that such combinations increase the likelihood of a thrombotic event, the labeling

[37] Of course, as the RADAR project acknowledges, there are limitations to its study and the ability to know for certain that the thrombotic events measured were in fact caused by the combination of Thalomid and other anti-cancer agents. That said, the comprehensive nature and scope of its review and the significance of its findings counsel against ignoring the project's conclusions out of hand.

misses a potentially critical opportunity to include information on the possible benefits of warfarin or low molecular weight heparin prophylaxis, information that could well protect patients from these potentially fatal adverse drug reactions.

It is unclear what, if anything, Celgene plans to do to modify Thalomid's labeling to reflect the increased risk of serious side effects the RADAR project demonstrated, particularly in light of Thalomid's inclusion as part of the Medicare Replacement Drug Demonstration Project. On Celgene's website -- which the company characterizes as "Under Construction" -- it does add some language regarding the use of Thalomid to treat cancer and other neoplastic conditions. Specifically, it states that "[p]atients with neoplastic and various inflammatory conditions being treated with thalidomide in combination with other agents may have an increased incidence of thrombo-embolic events such as pulmonary embolism, deep vein thrombophlebitis, thrombophlebitis, or thrombosis."

Although the transition from the "it is not known" language in Thalomid's labeling to the "may" language exhibited on the website shows that Celgene recognizes that there is a problem, the website's language is just as inadequate as that currently on Thalomid's labeling -- it does nothing to identify particular chemotherapy agents that pose especially heightened risks, nor does it recommend that prophylactic anticoagulation treatments be considered. In addition, the website information relating to thrombotic events is buried in a paragraph of miscellaneous adverse effects and no indication is given of the magnitude or potential severity of the increased risk.

Moreover, aside from its substantive inadequacies, the website information does little to help providers and patients presently considering whether to prescribe or take Thalomid. Most

healthcare providers and patients will, rightly, likely look to, and rely on, either the package insert or the Physician's Desk Reference[38], both of which indicate that "it is not known" whether concomitant therapy with Thalomid and other chemotherapy agents increases the risk of DVT/PE. Where both of those sources are consistent, many healthcare providers may see no apparent need to inquire further. Thus, for the precautionary information to be effective, it must at least be included in the labeling itself. That is particularly true here given the company's public statements, which could give the impression -- contrary to the website information and the overseas labeling that will be discussed in detail below -- that DVT/PE is not a significant issue.[39]

In contrast to Thalomid's current labeling and the language that appears on Celgene's website, the labeling used by Celgene's business partner Pharmion Corporation for the sale of Thalomid in Australia recognizes the problem head-on and provides a model that adequately informs patients of the concerns raised by the use of Thalomid to treat multiple myeloma and other malignant conditions. Pharmion's Thalidomide information brochure makes clear that "[i]n malignant conditions . . . patients are predisposed to a hypercoaguable state" and goes on to provide that "[c]aution should be used when Thalomid is combined with chemotherapy, as venous thromboembolism is a potential complication . . .. An unexpectedly high risk of venous thromboembolism has been observed when Thalomid is combined with chemotherapy for newly diagnosed patients with myeloma."[40] The brochure goes on to cite to studies showing that the

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[38] *Physicians' Desk Reference*, 1095-99 (59th ed. 2005).
[39] *See, e.g.*, Comments of Dr. Alan Lewis, Pres., Celgene San Diego, at the JMP Secs. LLC Research Conf., pp. 4-5 (Mar. 2, 2005) (discussing Thalomid's side effects months following the presentation of the RADAR paper and mentioning peripheral neuropathy and sedation but making no mention of DVT/PE; goes on to state that "the good news about Thalomid is there haven't been any new side effects that have been unearthed").
[40] *Thalidomide Pharmion Information Brochure*, pp. 34, 38-39, January, 2004.

potential for experiencing thrombotic events is particularly acute when Thalomid is used concomitant with vincristine, doxorubicin and dexamethasone.[41]

Unlike Thalomid's current U.S. labeling and Celgene's website, the brochure and Pharmion Thalidomide labeling make clear that the concurrent use of Thalomid and specific chemotherapy agents or corticosteroids among patients with multiple myeloma significantly increases the risk of thromboembolism. That information is valuable to both healthcare providers and patients in deciding how best to use Thalomid as part of a treatment regimen. Moreover, Thalomid's Australian information goes on to recommend that healthcare professionals consider the use of prophylactic anticoagulation treatments to limit the risk of DVT/PE. That information too is of critical importance to healthcare professionals in deciding whether to prescribe Thalomid to treat cancer and what measures should be taken to protect their patients from serious side effects. There simply is no valid reason -- given Thalomid's *actual profile* as a drug used almost exclusively to treat cancer -- why such critical information should not be made readily available.

B. Thalomid's Price Increases May Encourage Patients to Acquire the Drug from Foreign Pharmacies Outside the STEPS Program

For those patients without health insurance, and even for those who must pay a percentage of Thalomid's cost as coinsurance, the drug is very expensive. On an annualized basis, Thalomid costs approximately $24,098, or slightly more than a $2,000 monthly out-of-pocket cost for an uninsured cancer patient.[42] Of course, as with many medications, but perhaps more so with those similar to Thalomid, paying for the drug does not represent a discretionary

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[41] *Id.*, at p. 39

[42] This estimate is based on 100% of the Average Wholesale Price from the March 2004 **Redbook** for a typical dosage.

purchase, as the drug may literally be the difference between life and death. Therefore, for many patients, continued increases in the price of Thalomid, even small to modest price increases, will result in meaningful additional costs for the patient's necessary treatment.

Celgene is heavily dependent on its sales of Thalomid. Profits from Thalomid, which represented 81% of Celgene's 2004 revenues, are vital to the company's ability to make substantial investments in research and development of newer drugs in Celgene's product pipeline.[43] Net sales of Thalomid in 2004 increased 38% from 2003, and are up approximately 159% from 2002. According to the company's 2004 10-K annual reporting statement, these sales increases are "primarily" due to Thalomid price increases implemented in the second half of 2003 and the first nine months of 2004.[44] These prior year price increases were followed in February 2005 with a 10% increase in price for Thalomid's 200mg dosage, and a 20% increase for the drug's 50mg dosage. In addition, during an investors' conference held March 2, 2005, Celgene's President, Dr. Alan Lewis, indicated that the company intended to increase Thalomid's price again in 2005, most likely when the company receives its expected final FDA approval to expand the drug's indication to include multiple myeloma.[45] As a result, the price for Thalomid's 200mg dose blister pack has increased from an Average Wholesale Price ("AWP") of $78.75 in March, 2003 to $103.84 in April, 2005, an increase of 31%. Similarly, the price for the drug's 100mg dosage has increased from an AWP of $41.14 in March, 2003 to $70.47, in April, 2005, an increase of 71%. Finally, Celgene has raised Thalomid's 50mg dosage from an AWP of $21.48 in June, 2003 to $44.14 in April, 2005, an increase of 105%.

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[43] *See* Celgene Corp Form 10-K/A, p. 32, 35 (Filed March 21, 2005).
[44] *Id.*, at p. 35.
[45] Comments of Dr. Alan Lewis, Pres., Celgene San Diego, at the JMP Secs. LLC Research Conf., p. 5 (Mar. 2, 2005).

Celgene's ability to implement and sustain these price increases for Thalomid are due in large part to the Subpart H restricted distribution provisions imposed on the company when the FDA approved the drug in 1998.[46] Through this approval, Celgene was required to institute a risk management program -- the STEPS program -- to ensure safe distribution and use of the drug. While Thalomid's chemical entity -- thalidomide -- is itself a generic drug, Celgene has five United States' patents on the STEPS program which will not begin to expire until at least the year 2018.[47] By most accounts, the STEPS program has worked very well since Thalomid's launch. According to the FDA, instances of unintended pregnancy by women taking the drug -- the greatest risk due to Thalomid's teratogenicity -- have been extremely rare.[48] Given the heightened safety concerns posed by Thalomid and Celgene's success with the STEPS program, which, notwithstanding Celgene's patents, would be extremely expensive for a generic drug company to recreate, it is unlikely a generic drug manufacturer would seek to enter the market for thalidomide. Moreover, even if there were such a company considering the move, the FDA might be unwilling to approve an alternate drug distribution system.[49] Thus, absent competitive pressure from a competing drug, there are few impediments to Celgene's ability to continue to increase Thalomid's price and use those increased profits to fuel research and development on those additional drug's in the company's product pipeline.

Although troubling where access to a potentially life-saving drug is concerned, Celgene's unchecked Thalomid price increases would not usually fall within the province of the FDA to monitor and regulate. Here, however, there is a distinct possibility that continued increases in the price of Thalomid may have the unintended or unforeseen effect of driving

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[46] Title 21 CFR section 314.520 addresses drug approvals with restrictions to assure safe use.
[47] *See* Celgene Corp Form 10-K/A, p. 2 (Filed March 21, 2005).
[48] FDA, Joint Dermatologic and Ophthalmic Drugs & Safety and Risk Management Advisory Committee (February 26-27, 2004).
[49] *How Drug's Rebirth as Treatment For Cancer Fueled Price Increases*, *Wall Street Journal*, November 15, 2004.

patients to seek the drug from foreign pharmacies, where the cost may be less.[50] The concern, of course, is that by acquiring the drug from such sources, the patient may be operating outside of some or all of the safety checks built into the STEPS program, which could raise significant public health risks.

Indeed, the FDA warned consumers shortly after Thalomid's approval that they should not buy the drug over the internet because "you will bypass important safeguards designed to protect your health (and the health of others)."[51] In addition to the primary concern that a patient may not receive important safety information, counseling and monitoring required under STEPS; is the attendant concern that the drugs shipped from foreign sources may be different then the United States manufactured drug or counterfeit drugs with no therapeutic benefit and possible health risks. In fact, as recently as March 21, 2005, the FDA identified thalidomide as one of the drugs the agency placed on its import alert due to the FDA's determination that the drug is entering the United States and is being promoted for use in treating various diseases, including cancer.[52] The alert went on to state that "[d]ue to the serious health risks associated with this drug in inadequately controlled settings, it should be considered inappropriate" for importation under the FDA guidelines.

The obvious question here is whether the increase in illegal importation of thalidomide stems, at least in part, from the consistently increasing cost of the drug? If so, does the FDA's authority under Subpart H provide a means for the agency to restrict the ability of Celgene to continually increase the price of Thalomid? Certainly, drug approvals pursuant to Subpart H restricted distribution provisions are authorized to "assure safe use of the product". 21 CFR §

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[50] The petitioner is aware of at least one online foreign pharmacy that advertises thalidomide for sale without a prescription.
[51] Thalomid Consumer Information, available at: www.fda.gov/cder/news/thalinfo/thalomid.htm.
[52] Revision of Import Alert #66-41 "Unapproved New Drugs Promoted in the U.S.", March 21, 2005.

314.520(a). Limitations imposed by the FDA on the restricted drug's distribution must be commensurate with the safety concerns presented by the drug. 21 CFR § 314.520(b). And, finally, thalidomide in general, and Celgene's Thalomid in particular, are not just *any* drug, but one that has a documented history of causing significant risk if not used *exactly* as intended. With such risk comes a corporate responsibility to assure patients and the public that it will be marketed -- *and priced* -- with the highest commitment to safety. The commitment to safety is a charge to Celgene because, as the FDA stated in a letter to John Jackson, Celgene's Chairman and Chief Executive Officer, on April 21, 2000, "the need to provide and distribute thalidomide responsibly is essential to the public health."[53]

IV. CONCLUSIONS AND RECOMMENDATIONS

As the foregoing demonstrates, this situation represents a crossroads for the FDA's regulation of the sale of drugs to treat conditions for which the FDA has not assessed the drug's safety or efficacy through the new drug approval process. Few, if any, drugs are more dangerous than Thalomid (as its status as one of the most heavily regulated drugs ever approved indicates). Moreover, there are few, if any, drugs that are prescribed so infrequently for their approved indication and, at the same time, are prescribed so often -- and shown such promise -- for an indication that the FDA has not approved.

Thus far, the FDA's approach has been to treat Thalomid as though it was nothing more than a leprosy drug and effectively ignore the known fact that it is being used almost exclusively to treat cancer. This approach has worked well for Celgene. It has been able to generate hundreds of millions of dollars in revenues and pull itself into profitability based on the use of Thalomid to treat cancer, without having to directly address in its labeling the safety issues

[53] *See* FDA Warning Letter issued to Celgene Corporation, April 21, 2000.

attendant with that use. It has also been able to increase profits by continually raising prices, knowing that people with cancer will pay whatever they can to beat their disease, even though those price increases may drive patients out of the very safety system the FDA required as a condition for Thalomid's approval.[54]

Unfortunately, the FDA's approach has not worked well for patients. It has deprived them and their healthcare providers of critical information relating to the use of Thalomid to treat cancer, leaving them unnecessarily vulnerable to potentially fatal -- *and possibly preventable* -- side-effects.

It is not too late for the FDA to choose the right path and protect the patients who rely on the agency so heavily to protect their lives and health. Taking the actions requested in this petition will be an important step in that direction. They will help healthcare professionals and patients make a fully informed decision as to whether Thalomid is the right treatment for them and, if so, to take all appropriate precautions to ensure that this drug, so valuable to some patients,[55] does not harm the very people it is intended to save.

VII. ENVIRONMENTAL IMPACT

Petitioner believes the action requested in this Petition has no significant environmental impact.

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[54] *See, e.g.*, Comments of Dr. Alan Lewis, Pres., Celgene San Diego, at the JMP Secs. LLC Research Conf., pp. 4-5 (Mar. 2, 2005) (noting that when Thalomid was initially approved, it was intended to treat AIDS and Celgene "priced it accordingly"; goes on to state that once evidence showed that Thalomid was "a very effective oncology product," Celgene began "slowly increasing the price of the product to really reflect its value to the patient" and that "there is definitely likely to be a pricing increase this year"); Comments of John Jackson, CEO, Celgene Corp., at the Smith Barney Citigroup Healthcare Conf., p. 2 (Mar. 30, 2005) (noting, in discussing Celgene revenues, that "[p]rescription growth [for Thalomid] has clearly slowed. Fortunately, we're in a position where we've been able to significantly increase price").

[55] Again, as made clear above, this petition is in no way intended to limit patients' access to Thalomid for the treatment of cancer. Its goal is simply to ensure that healthcare providers and patients have all the information necessary to make an informed decision whether, and how, to include Thalomid in such a treatment regimen.

CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this Petition includes all information and views on which the Petition relies, and that it includes representative data and information known to the Petitioner which are unfavorable to the Petition.

Respectfully submitted,

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CITIZEN PETITION

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The following material does not contain confidential information and may be made available for public examination:

INDEX

1. *See, e.g.*, Comments of Bob Hugin, CFO, Celgene Corp., at the Lehman Bros. Global Health Care Conf.

2. Celgene's 2003 Annual Report.

3. RADAR Paper (DRAFT dated 3/5/2005)

4. Celgene Corp. Website *Thalomid*

5. *Thalidomide Pharmion Information Brochure,* January, 2004.

6. Comments of Dr. Alan Lewis, Pres., Celgene San Diego, at the JMP Secs. LLC Research Conf. (Mar. 2, 2005).

7. Comments of John Jackson, CEO, Celgene Corp., at the Smith Barney Citigroup Healthcare Conf. (Mar. 30, 2005).

8. Pannikar V., *The Return of Thalidomide: New Uses and Renewed Concerns,* World Health Org., Pharmaceuticals Newsletter, 2003, 2:11.

9. Centers of Disease Control Disease Info., *Hansen's Disease (Leprosy).*

10. *The News Hour with Jim Lehrer: Return of Thalidomide* (PBS television broadcast, Aug. 4, 1998).

11. Pan Am. Health Org., *No Role of Thalidomide in Leprosy*

12. Celgene Corp Form 10-K/A, p.35 (Filed March 21, 2005).

13. V. Chaudhry, MD *et al., Thalidomide-Induced Neuropathy, Neurology* 59:1982 (2002).

14. Zangari M. Anaissie, E., Barlogie B. et al. *Increased risk of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide and chemotherapy,* Blood 2001; 98:1614-1615..

15. Figg W, Arlen P, Gulley J, et al., *A Randomized Phase II Trial of Docetaxel (Taxotere) Plus Thalidomide in Androgen-Independent Prostate Cancer, Semin Oncol. 2001 (August); 28(suppl):62-66.*

16. *Physicians' Desk Reference*, 1095-99 (59th ed. 2005).

17. *How Drug's Rebirth as Treatment For Cancer Fueled Price Incrases, Wall Street Journal,* November 15, 2004.

18. AWP Information