CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-880

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-880

NAME OF APPLICANT / NDA HOLDER
Celgene Corporation

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
REVLIMID®

ACTIVE INGREDIENT(S)	STRENGTH(S)
1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisoindoline	5 mg and 10 mg

DOSAGE FORM
capsules for oral administration

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,635,517	06/03/1997	07/24/2016

d. Name of Patent Owner	Address *(of Patent Owner)*	
Celgene Corporation	86 Morris Avenue	
	City/State Summit/NJ	
	ZIP Code 07901	FAX Number *(if available)* (908) 673-2763
	Telephone Number (908) 673-9000	E-Mail Address *(if available)* gburton@celgene.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) ☞	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☑ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☑ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☑ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☑ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☑ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☑ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☑ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☑ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☑ Yes	☐ No
4.2 Claim Number (*as listed in the patent*) Claim 2	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☑ Yes ☐ No	
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)* Please see attachment for exemplary and relevant sections of proposed labeling.	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*	Date Signed
	3rd March 2005

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☑ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

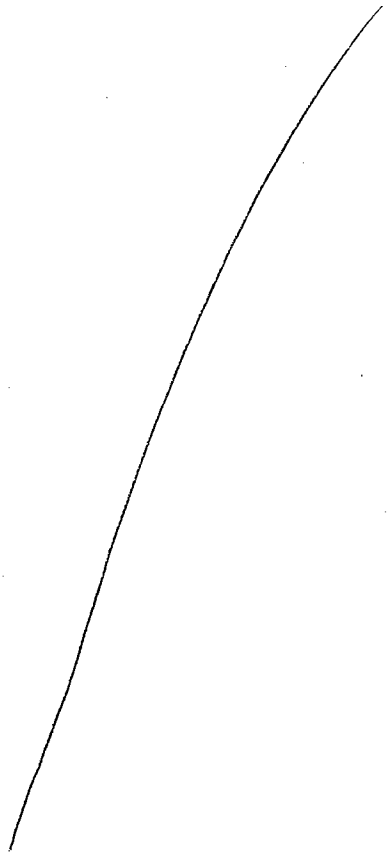
Name Celgene Corporation	
Address 86 Morris Avenue	City/State Summit/NJ
ZIP Code 07901	Telephone Number (908) 673-9000
FAX Number *(if available)* (908) 673-2763	E-Mail Address *(if available)* gburton@celgene.com

Mechanism of Action:
Lenalidomide affects a number of biological processes.

Lenalidomide inhibits the secretion of pro-inflammatory cytokines including TNF-a, IL-1ß, and IL-6 and IL-12 from LPS –stimulated PBMC[1,2]. Lenalidomide increases production of the anti-inflammatory cytokine IL-10 from LPS-stimulated PBMC, and consequently inhibits the expression but not the enzymatic activity of COX-2[3,4].

FORM FDA 3542a
QUESTION 4.2a
United States Patent No. 5,635,517
Celgene Corporation

Claim 2 is related to, for example, the following passages within the proposed labeling:



METHOD OF REDUCING TNFα LEVELS WITH AMINO SUBSTITUTED 2-(2,6-DIOXOPIPERIDIN-3-YL)-1-OXO-AND 1,3-DIOXOISOINDOLINES

The present invention relates a method of reducing levels of tumor necrosis factor α in a mammal through the administration of an amino substituted 2-(2,6-dioxopiperidin-3-yl) -1-oxoisoindolines and 1,3-dioxoisoindolines and to pharmaceutical compositions of such amino substituted indoline derivatives.

BACKGROUND OF THE INVENTION

Tumor necrosis factor α, or TNFα, is a cytokine which is released primarily by mononuclear phagocytes in response to a number immunostimulators. When administered to animals or humans, it causes inflammation, fever, cardiovascular effects, hemorrhage, coagulation, and acute phase responses similar to those seen during acute infections and shock states. Excessive or unregulated TNFα production thus has been implicated in a number of disease conditions. These include endotoxemia and/or toxic shock syndrome {Tracey et al., *Nature* 330, 662–664 (1987) and Hinshaw et al., *Circ. Shock* 30, 279–292 (1990)}; cachexia {Dezube et al., *Lancet*, 335 (8690), 662 (1990)} and Adult Respiratory Distress Syndrome where TNFα concentration in excess of 12,000 pg/mL have been detected in pulmonary aspirates from ARDS patients {Millar et al., *Lancet* 2(8665), 712–714 (1989)}. Systemic infusion of recombinant TNFα also resulted in changes typically seen in ARDS {Ferrai-Baliviera et al., *Arch. Surg.* 124(12), 1400–1405 (1989)}.

TNFα appears to be involved in bone resorption diseases, including arthritis. When activated, leukocytes will produce bone-resorption, an activity to which the data suggest TNFα contributes. {Bertolini et al., *Nature* 319, 516–518 (1986) and Johnson et al., *Endocrinology* 124(3), 1424–1427 (1989).} TNFα also has been shown to stimulate bone resorption and inhibit bone formation in vitro and in vivo through stimulation of osteoclast formation and activation combined with inhibition of osteoblast function. Although TNFα may be involved in many bone resorption diseases, including arthritis, the most compelling link with disease is the association between production of TNFα by tumor or host tissues and malignancy associated hypercalcemia {*Calci. Tissue Int.* (US) 46(Suppl.), S3–10 (1990)}. In Graft versus Host Reaction, increased serum TNFα levels have been associated with major complication following acute allogenic bone marrow transplants {Holler et al., *Blood*, 75(4), 1011–1016 (1990)}.

Cerebral malaria is a lethal hyperacute neurological syndrome associated with high blood levels of TNFα and the most severe complication occurring in malaria patients. Levels of serum TNFα correlated directly with the severity of disease and the prognosis in patients with acute malaria attacks {Grau et al., *N. Engl. J. Med.* 320(24), 1586–1591 (1989)}.

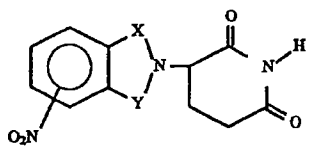
TNFα also plays a role in the area of chronic pulmonary inflammatory diseases. The deposition of silica particles leads to silicosis, a disease of progressive respiratory failure caused by a fibrotic reaction. Antibody to TNFα completely blocked the silica-induced lung fibrosis in mice {Pignet et al., *Nature*, 344:245–247 (1990)}. High levels of TNFα production (in the serum and in isolated macrophages) have been demonstrated in animal models of silica and asbestos induced fibrosis {Bissonnette et al., *Inflammation* 13(3), 329–339 (1989)}. Alveolar macrophages from pulmonary

sarcoidosis patients have also been found to spontaneously release massive quantities of TNFα as compared with macrophages from normal donors {Baughman et al., *J. Lab. Clin. Med.* 115(1), 36–42 (1990)}.

TNFα is also implicated in the inflammatory response which follows reperfusion, called reperfusion injury, and is a major cause of tissue damage after loss of blood flow {Vedder et al., *PNAS* 87, 2643–2646 (1990)}. TNFα also alters the properties of endothelial cells and has various pro-coagulant activities, such as producing an increase in tissue factor pro-coagulant activity and suppression of the anticoagulant protein C pathway as well as down-regulating the expression of thrombomodulin {Sherry et al., *J. Cell Biol.* 107, 1269–1277 (1988)}. TNFα has pro-inflammatory activities which together with its early production (during the initial stage of an inflammatory event) make it a likely mediator of tissue injury in several important disorders including but not limited to, myocardial infarction, stroke and circulatory shock. Of specific importance may be TNFα-induced expression of adhesion molecules, such as intercellular adhesion molecule (ICAM) or endothelial leukocyte adhesion molecule (ELAM) on endothelial cells {Munro et al., *Am. J. Path.* 135(1), 121–132 (1989)}.

Moreover, it now is known that TNFα is a potent activator of retrovirus replication including activation of HIV-1. {Duh et al., *Proc. Nat. Acad. Sci.* 86, 5974–5978 (1989); Poll et al., *Proc. Nat. Acad. Sci.* 87, 782–785 (1990); Monto et al., *Blood* 79, 2670 (1990); Clouse et al., *J. Immunol.* 142, 431–438 (1989); Poll et al., *AIDS Res. Hum. Retrovirus*, 191–197 (1992)}. AIDS results from the infection of T lymphocytes with Human Immunodeficiency Virus (HIV). At least three types or strains of HIV have been identified, i.e., HIV-1, HIV-2 and HIV-3. As a consequence of HIV infection, T-cell mediated immunity is impaired and infected individuals manifest severe opportunistic infections and/or unusual neoplasms. HIV entry into the T lymphocyte requires T lymphocyte activation. Other viruses, such as HIV-1, HIV-2 infect T lymphocytes after T cell activation and such virus protein expression and/or replication is mediated or maintained by such T cell activation. Once an activated T lymphocyte is infected with HIV, the T lymphocyte must continue to be maintained in an activated state to permit HIV gene expression and/or HIV replication. Cytokines, specifically TNFα, are implicated in activated T-cell mediated HIV protein expression and/or virus replication by playing a role in maintaining T lymphocyte activation. Therefore, interference with cytokine activity such as by prevention or inhibition of cytokine production, notably TNFα, in an HIV-infected individual assists in limiting the maintenance of T lymphocyte caused by HIV infection.

Monocytes, macrophages, and related cells, such as kupffer and glial cells, also have been implicated in maintenance of the HIV infection. These cells, like T cells, are targets for viral replication and the level of viral replication is dependent upon the activation state of the cells. {Rosenberg et al., *The Immunopathogenesis of HIV Infection*, Advances in Immunology, 57 (1989)}. Cytokines, such as TNFα, have been shown to activate HIV replication in monocytes and/or macrophages {Poli et al. *Proc. Natl. Acad. Sci.*, 87, 782–784 (1990)}, therefore, prevention or inhibition of cytokine production or activity aids in limiting HIV progression for T cells. Additional studies have identified TNFα as a common factor in the activation of HIV in vitro and has provided a clear mechanism of action via a nuclear regulatory protein found in the cytoplasm of cells (Osborn, et al., *PNAS* 86 2336–2340). This evidence suggests that a



II

The nitro intermediates of Formula II are known or can be obtained though conventional processes. For example, a nitrophthalic anhydride is allowed to react with α-aminoglutarimide hydrochloride {alternatively named as 2,6-dioxopiperidin-3-ylammonium chloride} in the presence of sodium acetate and glacial acetic acid to yield an intermediate of Formula II in which X and Y are both C=O.

In a second route, a lower alkyl ester of nitro-ortho-toluic acid is brominated with N-bromosuccinimide under the influence of light to yield a lower alkyl 2-(bromomethyl) nitrobenzoate. This is allowed to react with 2,6-dioxopiperidin-3-ammonium chloride in, for example, dimethylformamide in the presence of triethylamine to yield an intermediate of Formula II in which one of X is C=O and the other is CH_2.

The compounds of Formula I possess a center of chirality and can exist as optical isomers. Both the racemates of these isomers and the individual isomers themselves, as well as diastereomers when there are two chiral centers, are within the scope of the present invention. The racemates can be used as such or can be separated into their individual isomers mechanically as by chromatography using a chiral absorbant. Alternatively, the individual isomers can be prepared in chiral form or separated chemically from a mixture by forming salts with a chiral acid, such as the individual enantiomers of 10-camphorsulfonic acid, camphoric acid, α-bromocamphoric acid, methoxyacetic acid, tartaric acid, diacetyltartaric acid, malic acid, pyrrolidone-5-carboxylic acid, and the like, and then freeing one or both of the resolved bases, optionally repeating the process, so as obtain either or both substantially free of the other; i.e., in a form having an optical purity of >95%.

Alternatively, the compounds can be stereopreferentially synthesized by allowing the lower alkyl 2-(bromomethyl) nitrobenzoate intermediate discussed above to react with either (R)-1-benzyloxy-2,6-dioxo-3-tert.-butoxycarbonylaminopiperidine or (S)-1-benzyloxy-2,6-dioxo-3-tert.-butoxycarbonylaminopiperidine analogous to the method described by Robin et al., *Tetrahedron Asymmetry*, 6, 1249 (1995). Hydrogenation in this case not only reduces the nitro group to an amino group but also converts the N-benzyloxy group to an N-hydroxy group which can be removed with bromoacetophenone triethylamine and dimethylaminopyridine to yield the corresponding (R) or (S) enantiomer of Formula I.

The present invention also pertains to the physiologically acceptable non-toxic acid addition salts of the compounds of Formula I. Such salts include those derived from organic and inorganic acids such as, without limitation, hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulphonic acid, acetic acid, tartaric acid, lactic acid, succinic acid, citric acid, malic acid, maleic acid, sorbic acid, aconitic acid, salicylic acid, phthalic acid, embonic acid, enanthic acid, and the like.

Oral dosage forms include tablets, capsules, dragees, and similar shaped, compressed pharmaceutical forms containing from 1 to 100 mg of drug per unit dosage. Isotonic saline solutions containing from 20 to 100 mg/mL can be used for parenteral administration which includes intramuscular, intrathecal, intravenous and intra-arterial routes of administration. Rectal administration can be effected through the use of suppositories formulated from conventional carriers such as cocoa butter.

Pharmaceutical compositions thus comprise one or more compounds of Formula I associated with at least one pharmaceutically acceptable carrier, diluent or excipient. In preparing such compositions, the active ingredients are usually mixed with or diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule or sachet. When the excipient serves as a diluent, it may be a solid, semi-solid, or liquid material which acts as a vehicle, carrier, or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, elixirs, suspensions, emulsions, solutions, syrups, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders. Examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starch, gum acacia, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidinone, cellulose, water, syrup, and methyl cellulose, the formulations can additionally include lubricating agents such as talc, magnesium stearate and mineral oil, wetting agents, emulsifying and suspending agents, preserving agents such as methyl- and propylhydroxybenzoates, sweetening agents or flavoring agents.

The compositions preferably are formulated in unit dosage form, meaning physically discrete units suitable as a unitary dosage, or a predetermined fraction of a unitary dose to be administered in a single or multiple dosage regimen to human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with a suitable pharmaceutical excipient. The compositions can be formulated so as to provide an immediate, sustained or delayed release of active ingredient after administration to the patient by employing procedures well known in the art.

Oral dosage forms include tablets, capsules, dragees, and similar shaped, compressed pharmaceutical forms containing from 1 to 100 mg of drug per unit dosage. Isotonic saline solutions containing from 20 to 100 mg/mL can be used for parenteral administration which includes intramuscular, intrathecal, intravenous and intra-arterial routes of administration. Rectal administration can be effected through the use of suppositories formulated from conventional carriers such as cocoa butter.

Pharmaceutical compositions thus comprise one or more compounds of Formula I associated with at least one pharmaceutically acceptable carrier, diluent or excipient. In preparing such compositions, the active ingredients are usually mixed with or diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule or sachet. When the excipient serves as a diluent, it may be a solid, semi-solid, or liquid material which acts as a vehicle, carrier, or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, elixirs, suspensions, emulsions, solutions, syrups, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders. Examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starch, gum acacia, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidinone, cellulose, water, syrup, and methyl cellulose, the formulations can additionally include lubricating agents such as talc, magnesium stearate and mineral oil, wetting agents, emulsifying and suspending agents, preserving agents such as methyl- and propylhydroxybenzoates, sweetening agents or flavoring agents.

The compositions preferably are formulated in unit dosage form, meaning physically discrete units suitable as a

-continued

Constituents (for 1000 tablets)	
lactose	100.0 g
wheat starch	47.0 g
magnesium stearate	3.0 g

All the solid ingredients are first forced through a sieve of 0.6 mm mesh width. The active ingredient, lactose, magnesium stearate and half of the starch then are mixed. The other half of the starch is suspended in 40 mL of water and this suspension is added to 100 mL of boiling water. The resulting paste is added to the pulverulent substances and the mixture is granulated, if necessary with the addition of water. The granulate is dried overnight at 35° C., forced through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 6 mm diameter which are concave on both sides.

EXAMPLE 5

Tablets for chewing, each containing 75 mg of 1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisoindoline, can be prepared in the following manner:

Composition (for 1000 tablets)	
1-oxo-2-(2,6-dioxo-piperidin-3-yl)-4-amino-isoindoline	75.0 g
mannitol	230.0 g
lactose	150.0 g
talc	21.0 g
glycine	12.5 g
stearic acid	10.0 g
saccharin	1.5 g
5% gelatin solution	q.s.

All the solid ingredients are first forced through a sieve of 0.25 mm mesh width. The mannitol and the lactose are mixed, granulated with the addition of gelatin solution, forced through a sieve of 2 mm mesh width, dried at 50° C. and again forced through a sieve of 1.7 mm mesh width. 1-Oxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisoindoline, the glycine and the saccharin are carefully mixed, the mannitol, the lactose granulate, the stearic acid and the talc are added and the whole is mixed thoroughly and compressed to form tablets of approximately 10 mm diameter which are concave on both sides and have a breaking groove on the upper side.

EXAMPLE 6

Tablets, each containing 10 mg of 1-oxo-2-(2,6-dioxopiperidin-3-yl)-5-aminoisoindoline, can be prepared in the following manner:

Composition (for 1000 tablets)	
1-oxo-2-(2,6-dioxo-piperidin-3-yl)-5-amino-isoindoline	10.0 g
lactose	328.5 g
corn starch	17.5 g
polyethylene glycol 6000	5.0 g
talc	25.0 g
magnesium stearate	4.0 g
demineralized water	q.s.

The solid ingredients are first forced through a sieve of 0.6 mm mesh width. Then the active imide ingredient, lactose, talc, magnesium stearate and half of the starch are intimately mixed. The other half of the starch is suspended in 65 mL of water and this suspension is added to a boiling solution of the polyethylene glycol in 260 mL of water. The resulting paste is added to the pulverulent substances, and the whole is mixed and granulated, if necessary with the addition of water. The granulate is dried overnight at 35° C., forced through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 10 mm diameter which are concave on both sides and have a breaking notch on the upper side.

EXAMPLE 7

Gelatin dry-filled capsules, each containing 100 mg of 1-oxo-2-(2,6-dioxopiperidin-3-yl)-6-aminoisoindoline, can be prepared in the following manner:

Composition (for 1000 capsules)	
1-oxo-2-(2,6-dioxo-piperidin-3-yl)-6-amino-isoindoline	100.0 g
microcrystalline cellulose	30.0 g
sodium lauryl sulfate	2.0 g
magnesium stearate	8.0 g

The sodium lauryl sulfate is sieved into the 1-oxo-2-(2,6-dioxopiperidin-3-yl)-6-aminoisoindoline through a sieve of 0.2 mm mesh width and the two components are intimately mixed for 10 minutes. The microcrystalline cellulose is then added through a sieve of 0.9 mm mesh width and the whole is again intimately mixed for 10 minutes. Finally, the magnesium stearate is added through a sieve of 0.8 mm width and, after mixing for a further 3 minutes, the mixture is introduced in portions of 140 mg each into size 0 (elongated) gelatin dry-fill capsules.

EXAMPLE 8

A 0.2% injection or infusion solution can be prepared, for example, in the following manner:

1-oxo-2-(2,6-dioxo-piperidin-3-yl)-7-amino-isoindoline	5.0 g
sodium chloride	22.5 g
phosphate buffer pH 7.4	300.0 g
demineralized water	to 2500.0 mL

1-Oxo-2-(2,6-dioxopiperidin-3-yl)-7-aminoisoindoline is dissolved in 1000 mL of water and filtered through a microfilter. The buffer solution is added and the whole is made up to 2500 mL with water. To prepare dosage unit forms, portions of 1.0 or 2.5 mL each are introduced into glass ampoules (each containing respectively 2.0 or 5.0 mg of imide).

What is claimed is:

1. The method of reducing undesirable levels of TNFα in a mammal which comprises administering thereto an effective amount of a compound of the formula:

US006555554B2

(12) **United States Patent**
Muller et al.

(10) **Patent No.: US 6,555,554 B2**
(45) **Date of Patent: *Apr. 29, 2003**

(54) **ISOINDOLINES, METHOD OF USE, AND PHARMACEUTICAL COMPOSITIONS**

(75) Inventors: **George W. Muller**, Bridgewater, NJ (US); **David I. Stirling**, Branchburg, NJ (US); **Roger Shen-Chu Chen**, Edison, NJ (US)

(73) Assignee: **Celgene Corporation**, Warren, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/781,179**

(22) Filed: **Feb. 12, 2001**

(65) **Prior Publication Data**

US 2002/0045643 A1 Apr. 18, 2002

Related U.S. Application Data

(63) Continuation of application No. 09/543,809, filed on Apr. 6, 2000, now Pat. No. 6,281,230, which is a division of application No. 09/230,389, filed as application No. PCT/US97/13375 on Jul. 24, 1997, now abandoned, which is a continuation of application No. 08/690,258, filed on Jul. 24, 1996, now Pat. No. 5,635,517, and a continuation of application No. 08/701,494, filed on Aug. 22, 1996, now Pat. No. 5,798,368.

(60) Provisional application No. 60/048,278, filed on May 30, 1997.

(51) **Int. Cl.**[7] **A61K 31/454**; C07D 401/04

(52) **U.S. Cl.** **514/323**; 546/201

(58) **Field of Search** 514/323; 546/201

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(List continued on next page.)

Primary Examiner—Charanjit S. Aulakh
(74) *Attorney, Agent, or Firm*—Mathews, Collins, Shepherd & McKay, P.A.

(57) **ABSTRACT**

Substituted 1-oxo-2-(2,6-dioxopiperidin-3-yl)isoindolines are useful in reducing undesirable levels of TNFα in a mammal. Typical embodiments are pharmaceutical compositions containing 1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisoindoline and 1-oxo-2-(2,6-dioxo-3-methylpiperidin-3-yl)-4-aminoisoindoline.

17 Claims, No Drawings

EXCLUSIVITY SUMMARY

NDA # 21-880 SUPPL # HFD # 150

Trade Name Revlimid

Generic Name lenalidomide

Applicant Name Celgene Corporation

Approval Date, If Known January 7, 2006

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES ☐ NO ☐
Explain:

Investigation #2

IND # YES ☐ NO ☐
Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

Name of person completing form: Carl Huntley
Title: Regulatory Project Manager
Date: December 8, 2005

Name of Office/Division Director signing form: Robert Justice, MD
Title: Acting Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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
12/23/2005 06:59:20 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-880 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

Stamp Date: April 11, 2005 **PDUFA Goal Date:** October 7, 2005

HFD -150 **Trade and generic names/dosage form:** Revlimid (lenalidomide), 5 and 10 mg capsules

Applicant: Celgene Corporation **Therapeutic Class:** Immunomodulator

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

X **Yes. Please proceed to the next section.**

☐ **No. PREA does not apply. Skip to signature block.**

** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.*

Indication(s) ***previously approved*** **(please complete this section for supplements only):**

Each indication covered by this application must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): one (1)

Indication #1: For use in the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1 risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenic abnormality with or without additional cytogenetic abnormalities.

Is this an orphan indication?

X **Yes. PREA does not apply. Skip to signature block.**

☐ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

☐ **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**

☐ **Disease/condition does not exist in children**

☐ **Too few children with disease to study**

☐ **There are safety concerns**

☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____
Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Carl Huntley, R. Ph., MBA
Regulatory Project Manager

cc: NDA 21-880
HFD-960/ Rosemary Addy or Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(Revised 6-8-2005)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: N/A

Is this an orphan indication?

- ☐ **Yes. PREA does not apply. Skip to signature block.**
- ☐ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Carl Huntley, R. Ph., MBA_____
Regulatory Project Manager

cc: NDA 21-880
HFD-960/ Rosemary Addy or Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 6-8--2005)

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

/s/

Carl Huntley
6/23/05 02:03:32 PM

1.3.3 DEBARMENT CERTIFICATE

DEBARMENT CERTIFICATION

NDA- 21-880

Celgene Corporation hereby certifies that it did not, and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Graham Burton, FCRP, MBBS, FFPM
Sr. Vice President
Regulatory Affairs, Pharmacovigilance
and Project Managment

18th March 2005.
Date

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-880		Supplement Number	
Drug: Revlimid (Lenalidomide)		Applicant: Celgene Corporation	
RPM: Carl Huntley		HFD-150	Phone # 301-796-1372

Application Type: **(X)** 505(b)(1) **( )** 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** **( )** Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

❖ Application Classifications: 5010410	
• Review priority (re-submission)	**( )** Standard **(X)** Priority
• Chem class (NDAs only)	1
• Other (e.g., orphan, OTC)	Orphan (January 1, 2004) #03-1803
❖ User Fee Goal Dates	January 7, 2005 (10/07/05)
❖ Special programs (indicate all that apply)	**( )** None Subpart H **( )** 21 CFR 314.510 (accelerated approval) **(X)** 21 CFR 314.520 (restricted distribution) **(X)** Fast Track 4/11/03 **( )** Rolling Review **( )** CMA Pilot 1 **( )** CMA Pilot 2
❖ User Fee Information	
• User Fee	**( )** Paid UF ID number _____
• User Fee waiver	**( )** Small business **( )** Public health **( )** Barrier-to-Innovation **( )** Other (specify) _____
• User Fee exception	**(X)** Orphan designation **( )** No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) **( )** Other (specify) _____
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	**( )** Yes **(X)** No

• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	(X) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).* (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (3).* (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	( ) Yes ( ) No ( ) Yes ( ) No ( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*	
(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (5).*	( ) Yes ( ) No
(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No

❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	yes
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ **(X)** No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	May 26, 2005

General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE (September 30, 2005)
• Status of advertising (approvals only)	( ) Materials requested in AP letter (X) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None (X) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	yes
• Most recent applicant-proposed labeling	yes
• Original applicant-proposed labeling	
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	yes
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	yes
• Reviews	yes
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	yes
• Documentation of discussions and/or agreements relating to post-marketing commitments	yes
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	yes
❖ Memoranda and Telecons	yes
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	yes
• Pre-NDA meeting (indicate date)	
• Pre-Approval Safety Conference (indicate date; approvals only)	Regulatory Briefing 10/21/05
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	September 13, 2005
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	

Summary/Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	yes
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	Med TL, Medical Reviewer
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	PMC
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	In Review
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	N/A
❖ Demographic Worksheet *(NME approvals only)*	
❖ Statistical review(s) *(indicate date for each review)*	In Medical review
❖ Biopharmaceutical review(s) *(indicate date for each review)*	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	12/5/05
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	12/5/05
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	
❖ Facilities inspection (provide EER report)	Date completed: **(X)** Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	10/13/05
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	
❖ CAC/ECAC report	

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Celgene Corporation
86 Morris Avenue
Summit, New Jersey 07901
Tel 908-673-9000
Fax 908-673-9001

December 28, 2005

Robert Justice, M.D.
Acting Director, Division of Oncology Drug Products
Center for Drug Evaluation and Research / HFD-150
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705

NDA 21-880
REVLIMID® (lenalidomide)

RE: ACKNOWLEDGEMENT OF RECEIPT

Dear Dr. Justice:

On behalf of Celgene Corporation, I acknowledge that we have received the Action letter for NDA 21-880 dated December 27, 2005.

Thank you.

If you have any questions about this document or need further information, please contact me by telephone at (908) 673-9551, by facsimile at (908) 673-2763, or by email at gtoolan@celgene.com.

Sincerely,

Gretchen Toolan
Director, Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Celgene Corporation	December 28, 2005
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(908) 673-9000	(908) 673-2763
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
86 Morris Avenue Summit, NJ 07901	Not Applicable

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21 -880

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Lenalidomide	REVLIMID®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
3-(4'amino-1,3-dihydro-1-oxo-2H-isoindol-2-yl)-2,6-piperidinedione

CODE NAME *(If any)*
CC-5013,CDC-501,Imid 1, Imid 2, CI-B, Compound 8a, Revimid

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Capsule	5 and 10 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
REVLIMID ® is indicated for the treatment of patients with transfusion-dependent anemia due to low- or intermediate –1- risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Acknowledgement of Receipt

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

N/A

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND numbers: 60,100, —

DMF Numbers: —

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER:

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

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

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Gretchen Toolan	Gretchen Toolan, Director, Regulatory Affairs	December 28, 2005
ADDRESS *(Street, City, State, and ZIP Code)*		Telephone Number
86 Morris Avenue, Summit, New Jersey 07901		(908) 673-9551

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Celgene Corporation
86 Morris Avenue
Summit, New Jersey 07901
Tel 908-673-9000
Fax 908-673-9001

December 21, 2005

Robert Justice, M.D.
Acting Director, Division of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705

NDA 21-880
REVLIMID® (lenalidomide)

RE: RESPONSE TO FDA REQUEST FOR INFORMATION

Dear Dr. Justice:

Celgene Corporation (Celgene) received the minutes from our teleconference of December 20, 2005 to discuss the RevAssist[SM] Educational Program. Celgene agrees to the minutes, accepts all points noted and agrees to make the changes specified as part of the Final Printed Label.

If you have any questions about this submission or need further information, please contact me by telephone at (908) 673-9551, by facsimile at (908) 673-2763, or by email at gtoolan@celgene.com.

Sincerely,

Gretchen Toolan
Director, Regulatory Affairs

GT/es

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Celgene Corporation	December 21, 2005
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(908) 673-9000	(908) 673-2763
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
86 Morris Avenue Summit, NJ 07901	Not Applicable

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21 -880

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Lenalidomide	REVLIMID®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
3-(4'amino-1,3-dihydro-1-oxo-2H-isoindol-2-yl)-2,6-piperidinedione	CC-5013,CDC-501,Imid 1, Imid 2, CI-B, Compound 8a, Revimid

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Capsule	5 and 10 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

REVLIMID ® is indicated for the treatment of patients with transfusion-dependent anemia due to low- or intermediate –1- risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities

APPLICATION DESCRIPTION

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IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Response to FDA Request for Information

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

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Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

N/A

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IND numbers: 60,100. —

DMF Numbers: —

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☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
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CERTIFICATION

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2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

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

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
	Gretchen Toolan, Director, Regulatory Affairs	December 21, 2005

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
86 Morris Avenue, Summit, New Jersey 07901	(908) 673-9551

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

4 Page(s) Withheld

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

_✓_ § 552(b)(5) Deliberative Process

___ § 552(b)(5) Draft Labeling

CELGENE CORPORATION

Regulatory Affairs
86 Morris Avenue
Summit, NJ 07901

FAX TRANSMISSION SHEET

FAX NO: 908-673-2762

TO:	Carl Huntley
COMPANY:	FDA
FAX NO:	301-796-9845
NUMBER OF PAGES (Including Cover Sheet):	
DATE:	December 21, 2005
FROM:	Gretchen Toolan
TELEPHONE:	908-673-9551

If there are any problems, please call 908-673-9253

The following is Celgene's response to the fax sent to us on 20 December containing the Phase IV commitments.

APPEARS THIS WAY
ON ORIGINAL

Celgene Corporation
86 Morris Avenue
Summit, New Jersey 07901
Tel 908-673-9000
Fax 908-673-9001

Robert Justice, M.D.
Acting Director, Division of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705

December 21, 2005

NDA 21-880
REVLIMID® (lenalidomide)

RE: RESPONSE TO FDA REQUEST FOR INFORMATION

Dear Dr. Justice:

Celgene Corporation (Celgene) received a facsimile (fax) communication dated December 20, 2005 containing the 21 CFR 314.520 Subpart H post-marketing commitments. Celgene agrees to undertake each of the six commitments identified in the fax within the time-frames identified for those activities to be undertaken.

1). Embryo-fetal toxicity assessment commitment:
- Protocol Submission: by 06/06
- Study Start: by 09/06
- Final Report Submission: by 12/07

2). Study CC-5013-MDS-004 commitment:
- Protocol Submission: 03/05
- Study Start: 08/05
- Final Report Submission: by 12/08

3). Renal impairment assessment commitment:
- Protocol Submission: 11/04
- Study Start: by 03/06
- Final Report Submission: by 12/07

4). Submit Pregnancy Exposure follow-up plan commitment:
- Plan submission: 06/01/06

5). Submit evaluation plan of RevAssist^{SM} commitment:
- Plan submission: 06/01/06

6). Submit all exposed pregnancies within 15 days of receipt as 15 day expedited reports. This is acceptable to Celgene.

If you have any questions about this submission or need further information, please contact me by telephone at (908) 673-9551, by facsimile at (908) 673-2763, or by email at gtoolan@celgene.com.

Sincerely,

Gretchen Toolan
Director, Regulatory Affairs
GT/es

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT
Celgene Corporation

DATE OF SUBMISSION
December 21, 2005

TELEPHONE NO. *(Include Area Code)*
(908) 673-9000

FACSIMILE *(FAX)* Number *(Include Area Code)*
(908) 673-2763

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*
86 Morris Avenue
Summit, NJ 07901

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Not Applicable

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21 -880

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*
Lenalidomide

PROPRIETARY NAME *(trade name)* IF ANY
REVLIMID®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*
3-(4'amino-1,3-dihydro-1-oxo-2H-isoindol-2-yl)-2,6-piperidinedione

CODE NAME *(If any)*
CC-5013,CDC-501,Imid 1, Imid 2, CI-B, Compound 8a, Revimid

DOSAGE FORM:
Capsule

STRENGTHS:
5 and 10 mg

ROUTE OF ADMINISTRATION:
Oral

(PROPOSED) INDICATION(S) FOR USE:
REVLIMID ® is indicated for the treatment of patients with transfusion-dependent anemia due to low- or intermediate -1- risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities

APPLICATION DESCRIPTION

APPLICATION TYPE
(Check one)
☒ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)*
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Response to FDA Request for Information

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

N/A

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)
IND numbers: 60,100,
D bers:

ORM FDA 356h (4/03)

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER:

ERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

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

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Gretchen Toolan	Gretchen Toolan, Director, Regulatory Affairs	December 21, 2005

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
86 Morris Avenue, Summit, New Jersey 07901	(908) 673-9551

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I

DIVISION OF DRUG ONCOLOGY PRODUCTS

5901-B Ammendale Road
Beltsville, Maryland 20705

PHONE: (301) 796-1372 FAX: (301) 796-9867

TO: Gretchen Toolan
Director, Regulatory Affairs
Fax: 908-673-2763

FROM: Carl Huntley
Project Manager

Total number of pages, including cover sheet 3

Date: 12-20-05

COMMENTS: Regarding your New Drug Application 21-880 for Revlimid and post-marketing agreements.

Products approved under the accelerated approval regulations may require further studies to verify and describe the safety of the drug. This Subpart H post-marketing study commitment and the additional post-marketing study commitments, along with any completion dates agreed upon, are listed below. Please note that these are DRAFT recommendations until our action letter is finalized. Please respond, however, so that we may incorporate the language into the letter (along with the completion dates of the commitments).

1. The embryo-fetal toxicity assessment of Revlimid has not been adequately addressed. You will need to provide adequate information for this assessment in appropriate models that fully assesses the possible toxicity of Revlimid. These studies should be conducted in two different species that are appropriate to assess the full range of thalidomide embryo fetal effects. The rat is not an acceptable model. If the study with lenalidomide in the first species shows clear evidence of teratogenesis, than a confirmatory study will not be necessary. Although not generally considered "definitive" test systems for pharmaceutical products, additional studies of an exploratory nature on the embryo-fetal effects of lenalidomide (e.g. —— assay; —— assay), though not required, may be useful.

   Protocol Submission: by MM/YY
   Study Start: by MM/YY
   Final Report Submission: by MM/YY

In addition, we are asking for the following postmarketing study commitments that are not a condition of the accelerated approval. These commitments are listed below:

2. Submission of the study report and data from the ongoing study, CC-5013-MDS-004, a randomized, double-blind, placebo-controlled, multicenter, 3-arm study of the efficacy and safety of 2 doses of lenalidomide (5 mg daily versus 10 mg day 21 days of a 28 day cycle) versus placebo in red blood cell (RBC) transfusion-dependent patients with low-or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality when completed.

   Protocol Submission: 03/05
   Study Start: by MM/YY
   Final Report Submission: by MM/YY

3. Following Revlimid dosing, approximately 2/3 of lenalidomide is excreted as unchanged drug in urine. In multiple myeloma patients with mild renal impairment, exposure (plasma AUC) was 56% higher than in similar patients with normal renal function who received the same dose. Based on these data, you should conduct a study to determine the pharmacokinetics of lenalidomide in subjects with renal impairment. The study design should be consistent with the FDA Guidance, "Pharmacokinetics in Patients with Impaired Renal Function."

   Protocol Submission: by MM/YY
   Study Start: by MM/YY
   Final Report Submission: by MM/YY

4. Regarding the Pregnancy Exposure Follow-up Plan:

   Submit a Pregnancy Exposure follow-up plan which will document your plan to follow-up pregnancy exposures to outcome.

   Plan submission: 6/1/06

5. Regarding the RevAssist Evaluation/Surveillance Plan:

   Submit an Evaluation Plan of RevAssist to FDA within 3 to 6 months of approval. This should at a minimum include plans to study the Pharmacy Audit Plan, Outcomes of Pregnancy Exposures, and the Knowledge Surveys of physicians, nurses, and patients.

   Plan submission: 6/01/06

6. Submit all exposed pregnancies within 15 days of receipt as 15 day expedited reports.

Regards,
-carl

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

/s/

Carl Huntley
12/21/2005 07:59:47 PM
CSO

Celgene Corporation
86 Morris Avenue
Summit, New Jersey 07901
Tel 908-673-9000
Fax 908-673-9001

December 15, 2005

Robert Justice, M.D.
Acting Director, Division of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705

NDA 21-880
REVLIMID® (lenalidomide)

RE: RESPONSE TO FDA REQUEST FOR INFORMATION - REVASSIST[SM] RESTRICTED DISTRIBUTION PROGRAM

Dear Dr. Justice:

Celgene Corporation (Celgene) recently received Agency comments and requests regarding the REVLIMID® RevAssist[SM] program, in a FAX communication dated December 8, 2005. The FDA comments, and Celgene responses to these comments, are provided below.

FDA Comment:
"Please see below the educational materials that you referenced in an October 6 response. We would prefer that you submit all current educational materials into one submission. All primary educational materials (e.g., RevAssist Kit, "Getting Started with Revlimid") should describe the details of the RevAssist Program to the target audience. Any other material developed by you should at a minimum, reference the RevAssist Program." [*Followed by list of RiskMAP tools for physicians, patients, nurses and pharmacists*]

Celgene Response:
The requested materials are provided, as listed below. Additionally, following this letter is a table outlining the specific items provided, their item code (if applicable), a brief description of its role in the program, and the target audience.

For Physicians:

- The complete RevAssist[SM] Kit for health care providers is provided, including kit software, program overview (*RevAssist[SM] At-A-Glance*), prescriber guide (*RevAssist[SM] Prescriber Guide to English and non-English Materials*), draft package insert, prescriber instructions (*RevAssist[SM] Instructions for Providers*), prescriber registration (*RevAssist[SM] Prescriber Registration)*, REVLIMID® Patient Prescription Form, Guidelines for Ordering, Counseling and Dispensing REVLIMID®, the *RevAssist[SM] Patient Resource Pack* , and the Patient-Physician Agreement forms for all six patient categories. The physician and patient surveys are included in the Interactive Voice Response (IVR) software.

- Celgene Medical Information: please note that additional medical information materials, aside from the materials specifically referenced and included herein, will not be provided as a part of the RevAssist[SM] program. Requests for additional information from health care professionals will be addressed by the Celgene Medical Information staff who respond to questions using existing RevAssist[SM] educational materials.
- The prescribing guide (*Instructions for Prescribers*) is provided.
- The REVLIMID® clinical tool is provided.
- Physician FAQs have not been generated. A contact number is provided for assistance with any questions, in appropriate locations within all of these materials. When warranted, based on inquiries received, a FAQ document will be developed in the future.
- The Dosing Pocket Card is provided.
- The cytopenia management brochure (*Managing Neutropenia and Thrombocytopenia Associated with REVLIMID® Treatment for Patients with del 5q MDS)* is provided.

For Patients:

- The REVLIMID® Support Kit (including the draft Medication Guide, treatment planner, and calendar stickers) is provided.
- The RevAssist[SM] Kit contains the Patient Resource Pack for the patient (patient chart sticker, Planned Parenthood brochures, pocket guides (*Guide to Patient Surveys and Dosing for Patients with del 5q MDS*), and product patient brochure (*Important Information for Men and Women taking REVLIMID®*).
- The "Understanding Red Blood Cell Transfusions" patient brochure has been deleted from the materials for patients; instead, patients will receive "*Getting Started with REVLIMID®. A guide for deletion 5q MDS patients, their families, and caregivers*" which provides information specific to the treatment they will be receiving.
- Personal counseling with a consultant pharmacist is also a part of the RevAssist[SM] program; a copy of the script for this counseling is included as part of the pharmacy training documents.

For Nurses:

- The RevAssist[SM] Kit for health care providers, as provided here (see description under "For Physicians"), is intended to serve nurses as well as physicians.
- Celgene Medical Information: as noted previously, additional medical information materials (aside from the materials specifically referenced and included herein), will not be provided as a part of the RevAssist[SM] program. Requests for additional information from health care professionals will be addressed by the Celgene Medical Information staff who respond to questions using existing RevAssist[SM] educational materials.
- The prescribing guide (*A REVLIMID® Treatment Guide for del 5q MDS: A healthcare providers guide*) is included. Please note that the same brochure is used to serve both nurses and physicians.
- The REVLIMID® clinical tool is provided.

Item	Item Code	Description	Audience
RevAssist[SM] Kit	REV05068	Registration and education materials for the RevAssist[SM] program	Physicians, Patients, Nurses, and Pharmacists
REVLIMID Patient Physician Agreement Forms	(not numbered)	Part of the RevAssist[SM] program	Physicians, Patients
RevAssist[SM] Prescriber Registration Form	REV05076	Part of the RevAssist[SM] program	Physicians
RevAssist[SM] Instructions for Prescribers	REV05070	Part of the RevAssist[SM] program	Physicians
RevAssist[SM] Guidelines for Ordering, Counseling, and Dispensing	REV05075	Part of the RevAssist[SM] program	Pharmacists
REVLIMID® (lenalidomide) Patient Prescription Form	REV05071	Part of the RevAssist[SM] program	Physicians
RevAssist[SM] Education and Counseling Checklist for Pharmacies	REV05080	Part of the RevAssist[SM] program	Pharmacists
RevAssist[SM] Important Information for Men and Women Taking REVLIMID®	REV05072	Part of the RevAssist[SM] program	Patients
RevAssist[SM] Software and User Guide for REVLIMID® Patient-Physician Agreement Form	REV05069	Part of the RevAssist[SM] program	Physician
RevAssist[SM] CD-Rom Label for REVLIMID® Patient-Physician Agreement form	REV05069	Part of the RevAssist[SM] program	Physician
RevAssist[SM] At-A-Glance	REV05073	Part of the RevAssist[SM] program	Physician

Item	Item Code	Description	Audience
RevAssist[SM] Guide to Patient Surveys	REV05066	Part of the RevAssist[SM] program	Patients
RevAssist[SM] Patient Resource Pack	REV05064	Part of the RevAssist[SM] program	Patients
RevAssist[SM] Patient Chart Sticker	REV05067	Part of the RevAssist[SM] program	Physicians
RevAssist[SM] Prescriber Guide to English and non-English Materials	REV05065	Part of the RevAssist[SM] program	Physicians
REVLIMID® Clinical Tool	REV05011	Dosing, safety, efficacy from the registration trial	Physicians, Nurses
Dosing for Patients with del 5q MDS	REV05007	Dosing guidelines and cytopenia management	Physicians, Nurses
Managing Neutropenia and Thrombocytopenia Associated with REVLIMID® Treatment for Patients with del 5q MDS	REV05009	Cytopenia management	Physicians, Nurses
Getting Started With REVLIMID®--A Guide for del 5q MDS Patients, Their Families and Caregivers	REV05006	REVLIMID® education for patients who have been prescribed REVLIMID®	Patients
Getting Started With REVLIMID®--A Healthcare Providers Guide to Help Educate Patients with del 5q MDS About REVLIMID®	REV05019	Guide to help healthcare provider educate a patient who has been prescribed REVLIMID®	Physicians, Nurses
Patient Medication Guide	REV05016	REVLIMID® patient medication guide	Patients
A REVLIMID® Treatment Guide for del 5q MDS	REV05008	REVLIMID® prescribing guide the healthcare provider	Physicians, Nurses

Celgene Corporation
86 Morris Avenue
Summit, New Jersey 07901
Tel 908-673-9000
Fax 908-673-9001

December 15, 2005

Robert Justice, M.D.
Acting Director, Division of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705

NDA 21-880
REVLIMID® (lenalidomide)

RE: REVASSIST[SM] RESTRICTED DISTRIBUTION PROGRAM

Dear Dr. Justice:

Celgene Corporation (Celgene) recently received Agency comments and requests regarding the REVLIMID® RevAssist[SM] program, in a telephone contact between G. Toolan of Celgene and C. Huntley of the Agency on December 9, 2005; and a FAX communication dated December 12, 2005. The FDA comments, and Celgene responses to these comments, are provided below.

TELEPHONE CONTACT, DECEMBER 9, 2005:

FDA Request:
Please provide an updated Executive Summary of the RevAssist[SM] program reflecting its current components.

Celgene Response:
- An Executive Summary of the RevAssist[SM] program is provided.

FDA FAX COMMUNICATION, DECEMBER 12, 2005:

A total of 28 comments were originally conveyed by FAX on November 9, 2005, and Celgene responded to those comments on November 16, 2005. This December 12 communication addressed Celgene's responses.

We understand that FDA has determined that a number of these comments have been adequately addressed by Celgene's November 16 responses, and that no further action or discussion is required at this time with respect to comments 1-12, 14, 16, 18-21, 23, 24, and 26-28.

With respect to the remaining five comments, FDA's December 12, 2005 comments and Celgene's responses are provided below.

FDA Comment 13:
This is acceptable, however we note the following counseling requirements in S.T.E.P.S.® that won't be required in the RevAssist[SM] program:
- Not to extensively handle or open thalidomide
- Thalidomide is present in semen and risk to the fetus from the semen of male patients is unknown.

ODS is not aware of any reason for these requirements to be applied to lenalidomide and defers to DODP to decide on the need for this counseling to be done.

Celgene Response:
Celgene does not propose to change the planned patient counseling.

FDA Comment 15:
This is acceptable as long as these instructions are outlined in contracting pharmacies' Standard Operating Procedures. Celgene is encouraged to think about other scenarios that the consultant pharmacist could face that might require explicit instructions / procedures. Examples might include: - Unable to reach patient by telephone to counsel them. – Patient states that pregnancy tests were not conducted.

Celgene Response:
As per the requirements of the RevAssist[SM] program, which pharmacies will be required to follow by contract, patients will not receive drug if they do not receive required counseling or if there is any question as to whether required (negative) pregnancy tests were obtained. Celgene will ensure that contracted pharmacies have Standard Operating Procedures that are adequate to ensure compliance with RevAssist[SM] requirements.

FDA Comment 17:
ODS asks Celgene to develop a clear pregnancy exposure follow-up plan consistent with the S.T.E.P.S. program prior to approval. If adequate animal teratogenicity testing is reassuring about fetal risks such that the RevAssist program to prevent pregnancy exposures is discontinued, we recommend a pregnancy registry be established to monitor for potential human teratogenicity. Other components of the evaluation plan (voluntary follow-up survey and quarterly pharmacy audits) should be submitted within 6 months following product approval. ODS also asks that the company specifically describe how they will monitor the contracted pharmacies performance of the necessary risk management procedures, since the use of such pharmacies is different from S.T.E.P.S.

Celgene Response:
Celgene intends to implement the pregnancy exposure follow-up plan that is consistent with the plan in place for S.T.E.P.S.®. which applies to any information regarding the use of Celgene Corporation products during pregnancy. Information about use in pregnancy encompasses the entire course of pregnancy, the perinatal periods, and neonatal outcomes, even if completely normal and without adverse experiences.

If animal teratogenicity testing indicates that the RevAssist[SM] program monitoring for fetal exposure is unnecessary, Celgene will establish a pregnancy registry to monitor for potential human teratogenicity.

Celgene commits to submitting the voluntary follow-up survey and pharmacy audit protocol within 6 months following product approval.

Celgene wishes to clarify that we do not intend to perform on-site audits every quarter. The compliance of the contract pharmacies to the RevAssist^{SM} program will be assessed through on-site audits **within the first quarter** after the pharmacy's initial prescription. The audits will then be conducted at least annually for the first two years--the frequency will be adjusted based on the results of the initial audits.

FDA Comment 22:
Explain what the authorization form is for and why it is different from the Physician-Patient Agreement Form. We strongly recommend the Physician-Patient Agreement Form include or reference the medication guide or other source of complete safety information.

Celgene Response:
When told by the Agency to implement S.T.E.P.S.® in its entirety for REVLIMID®, Celgene approached this requirement from a literal point of view. The Authorization Form at the end of the package insert is part of the THALOMID® labeling negotiations legacy. If viewed by the Agency as redundant, Celgene is agreeable to deleting it from the label.

The proposed Physician-Patient Agreement Form (PPAF) included with this submission has been revised to prominently describe the three major warnings included in product labeling. It is however not intended to provide complete safety information. The Medication Guide, which is provided to patients and to health care providers, includes more complete safety information. To address this FDA comment, Celgene will add a sentence to the PPAF referencing the medication guide, as follows: "For further information, please see the REVLIMID® Medication Guide".

FDA Comment 25:
ODS and PLT recommend that the company clarify to the prescribing physician and to patients that are being counseled that if the planned parenthood brochure differs from the contraceptive methods recommended in the labeling, the labeling recommendations supersede recommendations in the planned parenthood brochure.

Celgene Response:
Celgene agrees to implement this recommendation, and will provide the clarification as described in FDA's comment.

If you have any questions about this submission or need further information, please contact me by telephone at (908) 673-9551, by facsimile at (908) 673-2763, or by email at gtoolan@celgene.com.

Sincerely,

Gretchen Toolan
Director, Regulatory Affairs
GT/es

REVLIMID® RISK MINIMIZATION ACTION PLAN: SUMMARY OF REVASSIST^{SM}

The RevAssist^{SM} program is a controlled distribution process designed to prevent fetal exposures pending further preclinical characterization of the teratogenic potential of lenalidomide. In addition, it addresses the risks of REVLIMID® therapy through education of physicians, other healthcare providers, and patients about potential cytopenias associated with REVLIMID® therapy.

1. Prescribing Program

1.1 General Requirements

Celgene Corporation (Celgene) will ensure that the following requirements are addressed by its Risk Minimization Action Plan, RevAssist^{SM}:

- REVLIMID® (lenalidomide) is only available under a special restricted distribution program called RevAssist^{SM}.
- Only prescribers registered with RevAssist^{SM} can prescribe REVLIMID® (lenalidomide).
- Only RevAssist^{SM} contract pharmacies can dispense REVLIMID® (lenalidomide).
- In order to receive REVLIMID® (lenalidomide), patients must enroll in RevAssist^{SM} and agree to comply with the requirements of the RevAssist^{SM} program.

1.2 Pharmacy Requirements

Celgene will limit the distribution of REVLIMID® through multiple contract pharmacies. The contract requires the following:

- All pharmacy distribution sites will be registered with the RevAssist^{SM} program.
- Pharmacy distribution sites will order REVLIMID® directly from Celgene's Customer Order Management center.
- Appropriate pharmacy staff will be trained by Celgene about the RevAssist^{SM} program requirements.
- Appropriate pharmacy staff will be trained by Celgene in adverse experience reporting procedures including immediate reporting of pregnancy.
- Pharmacists/nurses with a high level of expertise will educate patients and assist them with their disease management.
- Pharmacists/nurses will assist physicians and patients with compliance, counseling, educational materials, and medication delivery.

- Pharmacists/nurses will contact patients who have been prescribed REVLIMID® prior to shipping their prescription to ensure the patient has complied with all requirements of the program, including the need for the use of birth control and pregnancy testing (as applicable), and that the patient understands the risks associated with REVLIMID® (lenalidomide). No drug is to be shipped until this step occurs.
- Pharmacists will not ship REVLIMID® to a patient unless the pharmacist has received a confirmation number from the Celgene Customer Care Center.
- Pharmacists will not transfer REVLIMID® (lenalidomide) to another pharmacy.
- For each prescription filled, the pharmacists must comply with the RevAssist^{SM} dispensing requirements
    - Dispense no more than a 28-day supply.
    - Dispense with a REVLIMID® Medication Guide
    - Dispense only after receiving confirmation number from Celgene Customer Care Center.
    - Ship only after counseling patient.

1.3 Prescriber Requirements

Celgene will accept registration of prescribers who activate their registration by agreeing to the following:

- To comply with the RevAssist^{SM} program requirements.
- To counsel all patients on the benefits and risks of REVLIMID® (lenalidomide) therapy.
- To counsel female patients of childbearing potential to use two forms of contraception simultaneously and continuously for one month before therapy, during therapy, during dose interruptions, and for one month after REVLIMID® (lenalidomide) therapy unless the patient commits to continuous abstinence.
- To not prescribe REVLIMID® (lenalidomide) to any female patient of childbearing potential until verifying she has two negative pregnancy tests (one within 10-14 days and one within 24 hours) prior to writing the initial prescription. During the first month, verify negative pregnancy tests weekly and monthly thereafter if patient has regular menses; otherwise every 2 weeks if the patient has irregular menses.
- To instruct male patients to always use a latex condom every time they have sexual intercourse with a woman who is or can get pregnant, even if they have undergone a successful vasectomy.
- To report any pregnancy that occurs while a female patient is on REVLIMID® (lenalidomide) therapy, including during dose interruptions, and for one month after completion of therapy.
- To obtain the signed REVLIMID® Patient-Physician Agreement Form prior to obtaining REVLIMID® (lenalidomide).

- To obtain weekly blood tests during the first 8 weeks of REVLIMID® (lenalidomide) treatment and at least monthly thereafter to monitor for neutropenia and/or thrombocytopenia.

1.4 Patient Requirements

Celgene will accept registration for patients who meet the following conditions:

- Must be registered in the RevAssist^{SM} program.
- Must understand the potential for human birth defects if REVLIMID® (lenalidomide) is used by female patients who can become pregnant.
- Must sign a REVLIMID® Patient-Physician Agreement Form indicating the patient's understanding of the potential risks associated with REVLIMID® (lenalidomide) therapy.
- Must not share REVLIMID® with anyone.
- Must not donate blood or sperm while being treated with REVLIMID®.
- Must take part in mandatory, confidential surveys.
- Must discuss their REVLIMID® therapy with a RevAssist^{SM} contract pharmacy during their treatment and during dose interruptions.

In addition to the requirements listed for all patients above, female patients of childbearing potential must meet the following requirements:

- Must not be pregnant or breast-feeding.
- Must comply with the required pregnancy testing requirements throughout their REVLIMID® therapy.
- Must be capable of complying with the mandatory contraceptive measures for REVLIMD®, or commit to continuous abstinence from heterosexual intercourse.
- Must understand the responsibility to avoid pregnancy one month before therapy, during therapy, during dose interruptions, and for one month after REVLIMID® therapy.

2. Educational Program

Celgene will provide physicians, nurses, pharmacists and patients with educational materials on the benefits and risks associated with REVLIMID® therapy, contraception compliance, the requirements of the RevAssist^{SM} program.

2.1 Healthcare Provider Educational Materials

2.1.1 For Physicians:

- The complete RevAssist^{SM} Kit for health care providers includes:
    - Software CD-ROM with User Guide for REVLIMID Patient-Physician Agreement Forms,
    - program overview (*RevAssist^{SM} At-A-Glance*),

  - prescriber guide (*RevAssist^{SM} Prescriber Guide to English and non-English Materials*),
  - REVLIMID® package insert,
  - prescriber instructions (*RevAssist^{SM} Instructions for Providers*),
  - REVLIMID® Patient Prescription Form,
  - the *RevAssist^{SM} Patient Resource Pack*
- The REVLIMID® clinical tool.
- Physician Frequently Asked Questions (FAQs), as questions are generated.
- The Dosing Pocket Card
- The cytopenia management brochure (*Managing Neutropenia and Thrombocytopenia Associated with REVLIMID® Treatment for Patients with del 5q MDS).*

2.1.2 For Nurses

In addition to the items listed above, the following information is provided for nurses:

- The prescribing guide (*A REVLIMID® Treatment Guide for del 5q MDS: A healthcare providers guide*).
- Nurse FAQs, as questions are generated.
- The "*Getting Started with REVLIMID®. A healthcare provider's guide to help educate patients with del 5q MDS about REVLIMID®*" tool for nurses to utilize for patient education.

2.1.3 For Pharmacists

- The *Education and Counseling Checklist for Pharmacies.*
- Guidelines for Ordering, Counseling and Dispensing REVLIMID®,
- REVLIMID® Patient Prescription Form
- REVLIMID® Package Insert
- Question and answer document, to be generated as questions are raised.

2.2 Patient Educational Materials

- The REVLIMID® Support Kit (including the Medication Guide, treatment planner, and calendar stickers).
- The RevAssist^{SM} Kit includes the following information for patients:
  - Patient Resource Pack for the patient (patient chart sticker, Planned Parenthood brochures, pocket guides (*Guide to Patient Surveys and Dosing for Patients with del 5q MDS*), and
  - product patient brochure (*Important Information for Men and Women taking REVLIMID®*).
- "Getting Started with REVLIMID®. A guide for deletion 5q MDS patients, their families, and caregivers" which provides information specific to the treatment they will be receiving.

2.3 Additional Information Sources

- www.REVLIMID.com

- Celgene Customer Care Center: a call center designed to respond to healthcare provider, pharmacist, and patient questions and requests for information.
- Celgene Medical Services

3. Reporting

Celgene will report safety information as follows:

- Serious adverse drug experiences associated with the use of REVLIMID® in compliance with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).
- Rigorous investigation of adverse events through an Event Surveillance Plan that is intended to ensure that information on events of heightened surveillance is collected as consistently and comprehensively as possible. The "heightened surveillance" for REVLIMID® includes, but is not limited to:
    - Exposure in pregnancy
    - Neutropenia and/or thrombocytopenia-related adverse events
- A pregnancy exposure plan that applies to any information regarding the use of REVLIMID® during pregnancy. Information about use in pregnancy encompasses the entire course of pregnancy, including the perinatal period and neonatal outcomes, even if completely normal and without adverse experiences.
- [redacted]
- RevAssist℠ update reports to FDA (identical to S.T.E.P.S.® reporting requirements) with first report due 6 months after launch of REVLIMID® into interstate commerce. Includes:
    - Pregnancy exposures to REVLIMID® in U.S.
    - Fetal malformation reports resulting from pregnancy exposure to RELVIMID® in the U.S.

4. RevAssist℠ Program Evaluation

Celgene will conduct an evaluation of the RevAssist℠ program inpreventing fetal exposure. Features include:

- Voluntary Follow-up Survey
- Pharmacy audits are intended to assess the compliance of the contract pharmacies to the RevAssist℠ program. Each contracted pharmacy will be audited at least once during the first 3 months following their initial dispensing activities.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Celgene Corporation	December 15, 2005
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(908) 673-9000	(908) 673-2763
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
86 Morris Avenue Summit, NJ 07901	Not Applicable

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21 -880

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Lenalidomide	REVLIMID®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
3-(4'amino-1,3-dihydro-1-oxo-2H-isoindol-2-yl)-2,6-piperidinedione	CC-5013,CDC-501,Imid 1, Imid 2, CI-B, Compound 8a, Revimid

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Capsule	5 and 10 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

REVLIMID ® is indicated for the treatment of patients with transfusion-dependent anemia due to low- or intermediate –1- risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Response to FDA Request for Information – RevAssist℠ Restricted Distribution Program

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

N/A

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)
IND numbers: 60,100
DMF Numbers:

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER:

CERTIFICATION

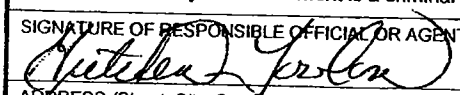
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

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

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
	Gretchen Toolan, Director, Regulatory Affairs	December 15, 2005

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
86 Morris Avenue, Summit, New Jersey 07901	(908) 673-9551

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

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Huntley, Carl

From: Gretchen Toolan [gtoolan@celgene.com]
Sent: Thursday, December 15, 2005 4:06 PM
To: Huntley, Carl
Subject: Revlimid proposed label-correction of typos

As we discussed, enclosed is a REVLIMID label containing typo corrections discovered during the SPL preparation process. The correction and line number are listed below:

- line 112/113 child bearing should be one word childbearing
- Line 244 add comma after range
- Line 245 add comma after range
- Line 255 add quotation marks around the words 'Boxed Warning'
- Line 283 add quotation marks around the words 'Boxed Warning'
- Line 319 add comma after range, remove the (before 8
- Line 320 add comma after range
- Line 381 add semi colon after X: remove semicolon after)parenthesis
- Line 431 changed 62/14/8 to 62/148
- Tables 4 and 5 renumbered to Tables 2 and 3
- Line 441 reference to table 4 and 5 need to be changed to 2 and 3
- Line 505 the word course in this table should be with an upper case C
- Line 508 the word course in this table should be with an upper case C
- Line 512 the word course in this table should be with an upper case C
- Line 514 the word course in this table should be with an upper case C
- Line 518 the word course in this table should be with an upper case C
- Line 592 added a space between REVLIMID and (lenalidomide)
- Line 604 corrected the phone number back to 1-888-668-2528
- Line 630 corrected the phone number back to 1-888-668-2528
- Line 656 health care should be one word healthcare
- Line 739 changed — to 28 day
- Line 747 remove comma at end of sentence and add a period
- Line 799 health care should be one word healthcare

Gretchen Toolan
Director, Regulatory Affairs
Celgene Corporation
86 Morris Avenue
Summit, NJ 07901
Telephone: 908.673.9551
Facsimile: 908.673.2762

<<Revlimid label proposed 12-15-05.doc>>

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 15, 2006

TO: Robert Justice, M.D., Director
Division of Oncology Drug Products (DODP), HFD-150

Richard Pazdur, MD, Director
Office of Oncology Drug Products (OODP), HFD-106

THROUGH: Anne Trontell, M.D., M.P.H., Deputy Director
Office of Drug Safety, HFD-400

FROM: Lenalidomide ODS RiskMAP Review Team

DRUG: Lenalidomide (Revlimid) Capsules

NDA: 21-880

SPONSOR: Celgene Corporation

SUBJECT: Review of Risk Mimimation Action Plan (RiskMAP) submitted September 30, 2005

PID: D050586

1 EXECUTIVE SUMMARY

This consult follows a request from the Division of Oncologic Drug Products for the Office of Drug Safety (ODS) to review, comment, and compare the Lenalidomide Risk Minimization Action Plan (RevAssist^{SM}) to the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.$^{®}$).

Lenalidomide is an immunomodulatory drug being developed for treatment of patients with transfusion-dependent anemia due to low- or intermediate-1 risk myelodysplastic syndromes (MDS). Because of the structural similarity between thalidomide and lenalidomide, there is a concern that this product carries the same risk for teratogenicity as has been demonstrated with thalidomide. The Sponsor was informed that until such time as more definitive animal studies rule out a risk for teratogenicity, a RiskMAP similar to S.T.E.P.S will be required for approval and marketing of lenalidomide.

We conclude that the RevAssist program overall looks comparable to S.T.E.P.S. based on the side-by-side comparison and therefore is acceptable to us for interim use until the questionable teratogenicity of lenalidomide is fully characterized and resolved. There are several outstanding issues that should be resolved prior to approval. The educational materials for patients and prescribers submitted to date do not adequately describe the RiskMAP components and requirements. The Sponsor should also submit a Pregnancy Exposure follow-up plan. A more complete list of comments and recommendations is included in section 7, pgs 9-10 of this document.

If animal or human teratogenicity is demonstrated, we would suggest the program be modified to reflect state-of-the-art pregnancy prevention risk management standards in pregnancy testing (e.g., sensitivity to 25 mIU/mL) and contraceptive methods (e.g. removal of all references to poorly effective contraceptive techniques such as the female condom), as well as a clear definition of females of child-bearing potential. Currently, the standards being implemented for the iPLEDGE program represent the Agency's recommendations of the best available standards. If adequate animal teratogenicity testing is reassuring about fetal risks such that the RevAssist program to prevent pregnancy exposures is discontinued, we recommend a pregnancy registry be established to monitor for potential human teratogenicity.

2 BACKGROUND

On December 22, 2004, Celgene Corporation submitted NDA 21-880 to the Agency for the use of lenalidomide for treatment of patients with transfusion-dependent anemia due to low- or intermediate-1 risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. Celgene requested and was granted permission to submit NDA 21-880 on a rolling basis. Lenalidomide was granted both fast track designation (granted April 11, 2003) and orphan drug status for the treatment of MDS (granted January 29, 2004).

The sponsor submitted the original RiskMAP on April 7, 2004 which included a proposal to educate health care providers and patients on the risk of cytopenias and the potential for teratogenicity and the need to minimize fetal exposure. At a meeting on August 23, 2005, Celgene mentioned their plans to limit the distribution of Revlimid through multiple specialty pharmacies.[1] Following the September 14, 2005 Oncology Drug Advisory Committee where the committee agreed that the benefit versus risk analysis warranted approval, the Agency and Celgene discussed the requirement that Revlimid must have a S.T.E.P.S. program because the reproductive/developmental toxicity studies were not adequate.[2] The Agency stated that revisions to the RiskMAP may be considered when additional pharmacology/toxicology information has been submitted and reviewed by the Agency. Celgene subsequently submitted the RiskMAP for Revlimid on September 30, 2005.

[1] Memorandum of Meeting Minutes, NDA 21-880; CAPT Carl Huntley, August 23. 2005.
[2] Memorandum of Meeting Minutes, NDA 21-880, CAPT Carl Huntley, September 20, 2005.

3 SAFETY CONCERNS

3.1 TERATOGENICITY

Teratogenic effects by Revlimid have not been demonstrated in rabbit and rat embryofetal development testing, however the Agency does not believe the embryo-fetal development in lenalidomide has not been adequately studied. Of major concern to the FDA is whether the structural similarity between thalidomide and lenalidomide may predict for the reproductive toxicity with this class of drugs. The most serious toxicity associated with thalidomide is its documented human teratogenicity. The risk of severe birth defects, primarily phocomelia or fetal death, is extremely high during the critical period of pregnancy.

3.2 CYTOPENIAS

In clinical studies in patients with MDS, the most common adverse events associated with the use of Revlimid® were thrombocytopenia and neutropenia; however, these events were generally manageable through dose reductions and dose interruptions.

4 PROPOSED RISK MINIMIZATION ACTION PLAN

4.1 OVERVIEW

Celgene proposes a RiskMAP for lenalidomide that is similar to the S.T.E.P.S. program. The goals of the RiskMAP are to:

- Educate physicians, other healthcare providers and patients that lenalidomide may cause fetal harm when administered to a pregnant woman
- Reduce the risk of fetal exposure from males taking REVLIMID who engage in sexual contact with a female partner of child bearing potential
- Educate physicians, other healthcare providers, and patients about potential cytopenias associated with REVLIMID therapy

Comment: The primary goal of the RiskMAP should be to prevent fetal exposures pending complete and adequate preclinical characterization of the teratogenic potential of lenalidomide. This comment was conveyed to the sponsor on November 9, 2005 and they agreed to this recommendation in their response on November 16, 2005.

A detailed side-by-side comparison of the two programs can be found in Appendix 1. Briefly, the key similarities and differences are as follows:

Key Similarities

- Both programs include mandatory registration of all patients, prescribers, and pharmacies (differences in pharmacy registration described below).

- Both programs identify six risk category groups[3]
- Both programs require pregnancy testing in all females of childbearing potential (differences in pregnancy testing described below).
- Both programs have an educational component for prescribers, pharmacists, and patients.
- Both programs do not allow refills and limit prescription to a 28-day supply.
- Both programs require an authorization/confirmation process in order to dispense drug product.

Key Differences

- Distribution System – direct mail shipment by Celgene contracted specialty pharmacy of every lenalidomide prescription with required telephone contact by consultant pharmacist. The S.T.E.P.S. program allows retail pharmacies to register with S.T.E.P.S. and face to face dispensing to occur.
- Pregnancy testing:
    - RevAssist requires two negative pregnancy tests at the initiation of therapy
- Packaging:
    - Revlimid Capsules will not have embossed pregnancy warning
    - No blister paks – Revlimid will be packaged in 30 and 100 count bottles
- Educational material does not include a video
- Education to patients through contracted pharmacies about cytopenias and the management of cytopenias

4.2 TOOLS

The RevAssist utilizes education of prescribers, pharmacists, nurses, and patients, as well as reminder tools (Patient Physician Agreement), and Performance-linked Access System (Celgene-contracted Specialty Pharmacies) that Celegene states will link distribution of lenalidomide to certain process safety measures.

Comment: Some details documenting this linkage have not yet been described by the sponsor and should be provided in the educational materials for physicians, pharmacists, and patients.

4.2.1 Education and Outreach

Physicians, pharmacists, nurses, and patients will receive educational materials on the potential lenalidomide risks with recommendations to educate patients that lenalidomide may cause human birth defects, and to effectively manage cytopenias during treatment. These educational tools include the following:

[3] Male children, female children not of childbearing potential, female children of childbearing potential, adult males, adult females not of childbearing potential, and adult females of childbearing potential.

For Physicians:

- RevAssist Kit (identical to S.T.E.P.S. except for program and product name) that includes Kit software, program overview, prescriber guide, PI, prescriber instructions, and physician and patient surveys
- Celgene Medical Information
- Physician information brochure (prescribing guide)
- Revlimid clinical tool
- Physician FAQs
- Dosing pocket card
- Cytopenia management brochure

For Patients:

- Revlimid Support Kit which includes a Medication Guide (originally proposed a patient information brochure), a treatment planner, and calendar stickers.
- RevAssist Kit to include patient chart sticker, planned parenthood brochures, pocket guide, product patient brochure
- Personal counseling with a consultant pharmacist

For Nurses:

- RevAssist Kit (identical to S.T.E.P.S. except for program and product name) that includes Kit software, program overview, prescriber guide, PI, prescriber instructions, and physician and patient surveys
- Celgene Medical Information
- Nurse information brochure (prescribing guide)
- Revlimid clinical tool
- Nurse FAQs
- Dosing pocket card
- Cytopenia management brochure
- "Getting Starting with Revlimid" a tool for nurses to utilize for patient education

For Pharmacists:

- RevAssist Kit (identical to S.T.E.P.S. except for program and product name) that includes Kit software, program overview, prescriber guide, PI, prescriber instructions, and physician and patient surveys
- Specifc training provided by Celgene and the specialty pharmacy
- Celgene Medical Information
- Pharmacy Checklist
- Educational materials
- Q&A reference document

Comments:

- *The current standard for RiskMAPs of this type includes a Medication Guide. Celgene has agreed to and has submitted a draft Medication Guide for review on November 16, 2005. A separate review has been completed by ODS/DSRCS[4].*
- *The educational materials for patients and prescribers submitted to date do not adequately describe the RiskMAP components and requirements. In their response to FDA on November 16, 2005, Celgene agreed that all commercial materials will reflect the final, approved label and the RiskMAP.*
- *ODS recommends (if concurrence by ORP) that educational materials be finalized prior to approval and that those materials be referenced or included in product labeling. We note that the iPLEDGE program was recently approved under Subpart H to prevent fetal exposures and that its educational program (actual titles of educational materials) is included as an enclosure in the action letter as well as in the Precautions section of the PI.*
- *S.T.E.P.S. and RevAssist are not as specific as iPLEDGE concerning appropriate contraceptive methods. If there are methods of birth control that aren't acceptable in RevAssist then this should be stated. The Sponsor may want to include a table of primary and secondary forms of acceptable birth control similar to the one in the isotretionoin labeling. Additionally, a Planned Parenthood brochure will be provided to prescribers as a tool for physicians to use should the physician do so. ODS and PLT recommend the company clarify to the prescribing physician and to patients that are being counseled that if the planned parenthood brochure differs from the contraceptive methods recommended in the labeling, the labeling recommendations supersede recommendations in the planned parenthood brochure.*
- *The RevAssist program focuses on prevention of pregnancy, however, Revlimid has other serious risks that would be important to convey to the patient, such as neutropenia, thrombocytopenia and infections. The proposed label contains information for the patient with an **Authorization** that the patient must sign. We suggest that the other serious risks with Revlimid be included as part of the information conveyed to the patient prior to signing of the Authorization.*

4.2.2 Reminder Tools

In additional to the educational materials listed above, the sponsor is requiring that physicians complete and return to the risk category specific patient registration and patient–physician agreement form.

Comments:

- *It is unclear what the authorization form is for (included at the end of proposed label) and how it differs from the Physician-Patient Agreement Form. This should be made clear.*

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[4] DSRCS Review of Medication Guide for Revlimid; Jeanine Best, M.S.N., R.N., P.N.P., Patient Product Information Specialist, DSRCS.; in DFS, dated December 7, 2005.

The sponsor does not plan to include the capsule embossing and blister pak that is currently utilized in the S.T.E.P.S. program.

4.2.3 Performance-linked Access System (e.g., Restricted Distribution)

With the exception of the controlled distribution through a Celgene-contracted specialty pharmacy, the process to obtain lenalidomide appears similar to the process currently used in the S.T.E.P.S. program. This process is briefly described below.

1. Physician counsels patient on possible risks associated with lenalidomide; no drug sharing, no blood or sperm donation, appropriate scheduled pregnancy testing and appropriate contraception requirements.
2. Physician performs pregnancy testing (if applicable).
3. Physician completes, prints, and signs the appropriate patient type RevAssist Patient Registration/Patient-Physician Agreement Form and faxes it to Celgene.
4. The patient is instructed to complete the phone survey by an interactive voice recognition (IVR) system prior to the prescriber obtaining an authorization number.
5. The physician completes a prescriber phone survey by IVR and obtains a new authorization number for each prescription. The following information is entered by the physician: prescribers DEA number, patient's SSN, pregnancy test results, average daily dose, and total number of days supplied. The authorization number from Celgene is included on the written prescription and Revlimid order form.
6. Prescriptions are faxed to Celgene contracted specialty pharmacy.
7. Prescriptions and authorization numbers valid for 7 days
8. Contracted pharmacist calls Celgene to confirm each authorization number; confirmation number is recorded on prescription by pharmacist.
9. Pharmacist will call patient to provide counseling and verify shipping address
10. Pharmacist must complete and sign Pharmacy Checklist
11. Dispense no more than 28 day supply
12. Telephone prescriptions are not allowed
13. No refill allowed – continuation of treatment requires new prescription and new activation

Comment:
It is not clear how the patient IVR response is known to the doctor and whether this interaction by the patient with the IVR is required in order for the prescriber to obtain an authorization number. The Sponsor needs to clarify this and we expect the educational materials to spell this out.

5 EVALUATION PLAN

The sponsor plans to evaluate pregnancy and grade 4 cytopenias and the effectiveness of the RevAssist will be evaluated by safety reporting, compliance measures, process measures and understanding of the educational information.

5.1 REPORTS ON PREGNANCY

The Sponsor plans to measure the number of exposed pregnancies and outcomes via spontaneous adverse event reports. They plan to

Comments:

- *The sponsor should submit a plan to follow-up on each pregnancy exposure to outcome.*
- *The occurrence of pregnancy exposures should be viewed as a serious adverse event. FDA should be notified of all exposed pregnancies within 15 days of receipt of information by Celgene. This comment was conveyed to the sponsor on November 9, 2005 and they agreed to this recommendation in their response on November 16, 2005.*
- *If animal teratogenicity is not demonstrated, and the RiskMAP is discontinued we recommend that the Sponsor submit a full Pregnancy Registry Protocol. This should be a formal protocol driven method or active surveillance for pregnancy exposures and for collection of data on pregnancy outcomes.*

5.2 REPORTS OF INFECTIONS AND HOSPITALIZATIONS DUE TO BLEEDING

Although prevention of infections and bleeding is not part of the RiskMAP, the Sponsor plans to measure the number these outcomes via spontaneous adverse event reports.

5.3 PROCESS MEASURES

The sponsor plans to conduct quarterly audits of the specialty pharmacies to determine whether there is consistency and adherence to the RevAssist Program.

Comment: We need a detailed plan of how the Sponsor will conduct and report on their plans to audit pharmacies (e.g., how can one determine if prescription was filled within 7 days, pregnancy test was conducted 24 hours before prescription written, etc). We recommend this be included as part of the Evaluation Plan.

5.4 UNDERSTANDING AND KNOWLEDGE ASSESSMENT

Understanding and Knowledge Assessment of physicians, patients, and nurses will occur via voluntary surveys.

Comment: We request additional details regarding the contents, timing, and reporting to FDA of the patient, physician, and nurse surveys and that these be submitted to FDA within 3 to 6 months of approval as part of the postmarketing commitment for an Evaluation Plan..

6 DISCUSSION/CONCLUSION

ODS conducted a review and a side-by-side comparison of the proposed RiskMAP for lenalidomide to the approved S.T.E.P.S. program for thalidomide and conclude that the RevAssist program overall looks comparable to S.T.E.P.S. The key difference is the way the product is to be distributed. Under S.T.E.P.S., thalidomide can be distributed to and dispensed by any pharmacy registered in the S.T.E.P.S. program. Under RevAssist, lenalidomide will only be distributed to and dispensed by direct mail shipment by a Celgene-contracted specialty pharmacy. The RevAssist program also requires two negative pregnancy tests at the initiation of therapy; in contrast to only one negative pregnancy test under S.T.E.P.S. Additionally, lenalidomide capsules will not have embossed pregnancy warning, and the capsules will be packaged in 30 and 100 count bottles which are in contrast to embossed capsules and blister pak for thalidomide. Finally, the educational materials for lenalidomide do not include a video.

The current proposed RiskMAP (RevAssist) is acceptable to us for interim use until the questionable teratogenicity of lenalidomide is fully characterized and resolved and pending review of the educational materials. However, if animal or human teratogenicity is demonstrated, we would suggest the program be modified to reflect state-of-the-art pregnancy prevention risk management standards in pregnancy testing (e.g., sensitivity to 25 mIU/mL) and contraceptive methods (e.g. removal of all references to poorly effective contraceptive techniques such as the female condom), and clear definition of females of child-bearing potential. Currently the standards being implemented for the iPLEDGE program represent the Agency's recommendations of the best available standards). If adequate animal teratogenicity testing is reassuring about fetal risks such that the RevAssist program to prevent pregnancy exposures is discontinued, we recommend a pregnancy registry be established to monitor for potential human teratogenicity.

7 COMMENTS/RECOMMENDATIONS FOR DOPD AND/OR SPONSOR

The following are comments on RiskMAP issues that have not been resolved at the time this document has been finalized. We anticipate providing further comment following submission of the educational materials. Please see appendices 2 and 3 for earlier comments on the RiskMAP that already been shared with DOPD and the Sponsor.

Regarding the Educational Plan

- Please refer to comments and recommendations in DSCRS review of the Medication Guide.[5]
- We request that Celgene submit all current educational materials into one submission. All primary educational materials (e.g., RevAssist Kit, "Getting Started with Revlimid") should describe the details of the RevAssist Program to the target audience. Any other material developed by the sponsor should at minimum reference the RevAssist Program. ODS will review these materials to ensure that they are factually correct and complete with regard to the RevAssist Program.

[5] DSRCS Review of Medication Guide for Revlimid; Jeanine Best, M.S.N., R.N., P.N.P., Patient Product Information Specialist, DSRCS.; in DFS, dated December 7, 2005.

- S.T.E.P.S. and RevAssist are not as specific as iPLEDGE concerning appropriate contraceptive methods. If there are methods of birth control that aren't acceptable in RevAssist then this should be stated. The Sponsor may want to include a table of primary and secondary forms of acceptable birth control similar to the one in the isotretinoin labeling. Additionally, a Planned Parenthood brochure will be provided to prescribers as a tool for physicians to use should the physician do so. ODS and PLT recommend the company clarify to the prescribing physician and to patients that are being counseled that if the planned parenthood brochure differs from the contraceptive methods recommended in the labeling, the labeling recommendations supersede recommendations in the planned parenthood brochure.
- The RevAssist program focuses on prevention of pregnancy, however, Revlimid has other serious risks that would be important to convey to the patient, such as neutopenia, thrombocytopenia and infections. The proposed label contains information for the patient with an **Authorization** that the patient must sign. We suggest that the other serious risks (neutropenia, thrombocytopenia, and DVTs) with Revlimid be included as part of the information conveyed to the patient prior to signing of the Authorization

Regarding the Evaluation/Surveillance Plan

- Pregnancy Exposure follow-up plan – we note the Sponsor's commitment to promptly notify the Agency of exposure, but we do not see plan to follow-up pregnancy exposures to outcome. The sponsor should submit their plans to do follow-up as part of the Evaluation Plan requested as a postmarketing commitment (see below).
- A postmarketing commitment should be required of the Sponsor to submit an Evaluation Plan of RevAssist to FDA within 3 to 6 months of approval. This should at a minimum include plans to study the Pharmacy Audit Plan, Outcomes of Pregnancy Exposures, and the Knowledge Surveys of physicians, nurses, and patients.
- FDA should be notified of all exposed pregnancies within 15 days of receipt by the Sponsor. These reports should be submitted as 15 day expedited reports. This comment was conveyed to the Sponsor on November 9, 2005 and they agreed to this recommendation in their response on November 16, 2005.We recommend to DODP that this commitment be documented in the action letter.

Future RiskMAP modifications

- If animal or human teratogenicity is demonstrated we recommend the following RiskMAP enhancements:
  - Regarding pregnancy testing - The current standard is that pregnancy tests have a sensitivity of 25mIU/mL and that pregnancy testing be conducted in a CLIA certified laboratory.
  - Regarding the definition of "adult females not of child bearing potential" - the current proposal by Celgene is to use the same definitions that are being used in S.T.E.P.S. This is acceptable for the interim program, however if animal or human teratogenicity is demonstrated for lenalidomide, the definition of FDBP will need to be modified to bring it up to current standards.

- Regarding Contraceptive Counseling – contraceptive counseling materials recommended in some of the educational materials do not appear to be acceptable. Contraceptive educational materials will need to be modified to assure that patients and clinicians are informed about acceptable effective contraceptive practices.

- If animal teratogenicity is not demonstrated, and the RiskMAP is discontinued, we recommend that the Sponsor submit a full Pregnancy Registry Protocol. This should be a formal protocol driven method or active surveillance for pregnancy exposures and for collection of data on pregnancy outcomes.

Appendix 1. Comparison of RevAssist and S.T.E.P.S.		
Components	**RevAssist**	**S.T.E.P.S.®**
Approval of drug products under:	Subpart H (21 CFR 314.5)	Subpart H (21 CFR 314.5)
RiskMAP goal(s)	1. Educate physicians, other healthcare providers and patients that lenalidomide may cause fetal harm when administered to a pregnant woman 2. Reduce the risk of fetal exposure from males taking REVLIMID who engage in sexual contact with a female partner of child bearing potential 3. Educate physicians, other healthcare providers, and patients about potential cytopenias associated with REVLIMID therapy	Prevention of fetal exposures
Boxed Warning	Yes	Yes
Pregnancy Category	X	X
Medication Guide	Yes	No
Performance-linked access system (e.g., Restricted Distribution Program)	Yes Distribution to Contracted specialty pharmacies	Yes Distribution to Registered Pharmacies
Patients Registered	Yes	Yes
Prescribers Registered	Yes	Yes
Pharmacies Registered	Yes	Yes
Pharmacist interaction with patient at time of dispensing	Telephone contact with pt to provide additional education on birth defects and other information prior to shipment of medication	Face to face contact with patient
Pregnancy Testing Required	Pregnancy tests (sensitivity at least 50mIU/ml) as follows:	Pregnancy tests (sensitivity at least 50mIU/ml) as follows:
	Women of childbearing potential **2 tests** within 10-14 days and within 24 hours of starting thalidomide, and then	Women of childbearing potential within 24 hours of starting thalidomide, and then
	Weekly during 1st four weeks of therapy, then	Weekly during 1st four weeks of therapy, then

Appendix 1. Comparison of RevAssist and S.T.E.P.S.		
Components	**RevAssist**	**S.T.E.P.S.®**
	Every 4 weeks in women with regular menstrual cycles.	Every 4 weeks in women with regular menstrual cycles.
	If menstrual cycles are irregular then pregnancy testing every 2 weeks	If menstrual cycles are irregular then pregnancy testing every 2 weeks
	Report date and result of last pregnancy into prescriber IVR with each Rx	Report date and result of last pregnancy into prescriber IVR with each Rx
Contraception required	For Females of Child Bearing Potential (FCBP) – One highly effective[6] and one other method at the same time for 4 weeks before, during, during dose interruptions and 4 weeks after lenalidomide.	For Females of Child Bearing Potential (FCBP) – One highly effective[6] and one other method at the same time* for 4 weeks before, during and 4 weeks after thalidomide.
Male Patients	Required to always use a latex condom during intercourse with any FCBP, even if the male has undergone a successful vasectomy	Required to always use a latex condom during intercourse with any FCBP, even if the male has undergone a successful vasectomy.
Reporting of Pregnancies	• Suspected fetal exposure –report to FDA and Celgene, refer pt to OB •	Prescriber report immediately to the FDA via MedWatch, and to Celgene and refer to OB
Patient Counseling/Educational Materials	• Required. Patient brochure; • No video • "Unique to RevAssist, pharmacist will call pt, document on pharmacy checklist prior to shipment [RiskMAP p 10 & 17]	Required. Patient brochure, video
IVR - Patients	Monthly for FCBP and male pts Every 6 months for females NCBP	Monthly for FCBP and male pts Every 6 months for females NCBP
Informed Consent Forms	Prescriber reviews and signs Patient-Physician Agreement Form and faxes to Celgene prior to Rx ,	Prescriber reviews with pt. All patients must complete and sign patient registration and informed consent form

[6] Highly effective methods are tubal ligation, partner's vasectomy, hormonal contraception, IUD), the second form of contraception can be latex condom, diaphragm, cervical cap.

Appendix 1. Comparison of RevAssist and S.T.E.P.S.		
Components	**RevAssist**	**S.T.E.P.S.®**
Process to obtain Revlimid (Prescription Requirements)	• Authorization number from Celgene to prescriber to be written on Rx and Revlimid order form after prescriber completes IVR – different auth # for each Rx; can fax Rx and order form to pharmacy • Prescriptions are faxed to pharmacy • Confirmation number from Celgene obtained by pharmacist and recorded on Rx • Dispense no more than 28 day supply • Prescriptions and authorization numbers valid for 7 days • Pharmacist will call pt to provide counseling and verify shipping address • Pharmacist must complete and sign Pharmacy Checklist • Telephone prescriptions are not allowed • No refill allowed – continuation of treatment requires new prescription and new activation	• Activate every prescription by accessing Celegene (telephone) • Record confirmation number on the prescription • Accept prescription only if it has been written within the previous 7 days. • Dispense no more than a 4 week (28 day supply) • Dispense blister packs intact – no repackaging allowed. • Dispense further prescriptions only if fewer than 7 days remains on the previous prescription • Telephone prescriptions are not allowed • No refill allowed – continuation of treatment requires new prescription and new activation
Drug order form	Prescriber fills out Revlimid order form after obtaining auth # and faxes it to pharmacy	Unknown if S.T.E.P.S. utilizes order form
Pharmacy & Pharmacy Audits to measure compliance with requirements of RevAssist	Celgene-contracted specialty pharmacies; audits of pharmacy w/in 1st quarter then annually "for the first 2 years	Retail pharmacies with dispensing pharmacists registered in S.T.E.P.S.
Special Product packaging	• </= 28 day supply (from pharmacy bottle of 30-100 caps) • "Do Not Get Pregnant" stickers on dispensed bottles • No pictures of thalidomide babies on lenalidomide materials	• 28 day blister pack with additional safety information • "No pregnancy" embossing on capsules

Appendix 2. Revlimid Riskmap (Revassist) Comments and Recommendations by ODS and PLT (faxed to Celgene on November 9, 2005)

We have reviewed the most recent submission of October 6, 2005 and have a number of critical comments and questions that need a sponsor response. In addition to these, we request any sponsor response to our critical questions and comments also include an explicit and detailed side-by-side comparison of RevAssist to S.T.E.P.S.. In our review, we found multiple areas of ambiguity where we could not determine whether RevAssist diverged from current S.T.E.P.S. procedures.

In addition to these critical comments, we have a number of important comments and questions for which we seek a sponsor response.

Critical RiskMAP Elements to be addressed by the sponsor

- The primary goal of the RiskMAP should be to prevent fetal exposures pending complete and adequate preclinical characterization of the teratogenic potential of lenalinomide.
- The RiskMAP should be included in final approved labeling.
- All educational materials for patients and providers need to describe the RiskMAP. (We note that the patient brochure, "Getting started with Revlimid" does not mention the need for contraception and pregnancy testing.)
- The current standard for RiskMAPs of this type includes a Medication Guide.
- The current pregnancy test schedule as proposed by the sponsor is inadequate. Either the pregnancy test schedule of the current S.T.E.P.S. program or the one outlined in the current iPLEDGE program for isotretinoin should be followed.
- Provide clarification on the following items regarding registration/distribution process:
    - Whether each patient is registered one time and followed longitudinally or whether registration of the patient occurs with each prescription.
    - How pregnancy test results are communicated to the pharmacist so that the prescription can be filled. Does the existence of an authorization number on the prescription mean that the pregnancy test was negative? Or does obtaining a confirmation number by the pharmacist mean the pregnancy test result was negative?
    - How and where are the results of the pregnancy tests and contraceptive methods used documented, especially for evaluation of the RiskMAP program? How is there assurance that pregnancy testing results will be verified by a physician and appropriately timed? Are home pregnancy tests acceptable in this program?
    - The "7-day window" for dispensing lenalidomide should be linked explicitly to the date of the performance of the last pregnancy test. As currently stated, it is unclear whether and how the most recent pregnancy test is in any way coupled to the date that the prescription for lenalidomide is written and transmitted. The pregnancy test result is the most important aspect of the RiskMAP for assuring that physicians do not prescribe and

pharmacists do not dispense lenalidomide to women with an on-going pregnancy.

- Please clarify the prescribing physician's responsibility for contraceptive counseling, monitoring of compliance with birth control methods, and review/ reporting of pregnancy test results and how this will be documented to the RiskMAP program. In addition, please clarify how such participation will be documented and how often this documentation to the RiskMAP program will occur. How does the sponsor plan to monitor compliance with these critical issues?
- Will Revlimid ONLY be shipped to the patient by the pharmacist or can the patient go to the pharmacy and have face-to-face counseling, receive the new patient educational materials, and pick up the drug?
- Please clarify what the consultant pharmacist is supposed to do in the event that they determined that the FCBP is not and has not been on appropriate contraception.
- We ask to review the physician and patient IVR survey questions for their acceptability.

- Submit details regarding your evaluation plan; specifically your:
  - Pregnancy Registry Protocol and Pregnancy Exposure Follow-up plan
  - Voluntary Follow-up Survey for patients, physicians, and nurses
  - Quarterly pharmacy audits protocol
- The occurrence of pregnancy exposures should be viewed as a serious adverse event. FDA should be notified of all exposed pregnancies within 15 days of receipt of information by Celgene.

Important Comments/Questions regarding proposed RiskMAP

General

- The issue of which patients should be considered "adult females not of childbearing potential" has not been adequately addressed in the Revlimid RiskMAP or the educational materials. A definition of women who fall into this category is required. Definitions that would be acceptable and consistent with the current iPLEDGE program are as follows:

  All adult women are considered females of childbearing potential (FCBP) if they have NOT previously been documented to have either:

  (A) a hysterectomy or
  (B) menopause

  Menopause is assumed to have occurred in a woman when there is either:

  (a) appropriate medical documentation of prior complete bilateral oophorectomy (i.e., surgical removal of the ovaries, resulting in "surgical menopause"), or

  (b) permanent cessation of previously occurring menses as a result of ovarian failure with documentation of hormonal deficiency* by a certified

healthcare provider (i.e., "spontaneous menopause", which occurs in the United States at a mean age of 51.5 years).

*Hormonal deficiency should be appropriately documented in the case of suspected spontaneous menopause as follows:

(1) If age >54 years and with the absence of normal menses: Serum FSH (Follicle Stimulating Hormone) level elevated to within the post-menopausal range based on the laboratory reference range where the hormonal assay is performed;

(2) If age <54 years and with the absence of normal menses: Negative serum or urine β-HCG with concurrently elevated serum FSH (Follicle Stimulating Hormone) level in the post-menopausal range, depressed estradiol (E_2) level in the post-menopausal range, and absent serum progesterone level, based on the laboratory reference ranges where the hormonal assays are performed.

- Please completely describe the Revilimid RiskMAP in the text of the documentation. References to the labeling and brochures may be included in the text.
- Please make all portions of the RiskMAP document consistent. For example, there are discrepancies between the overall description of RevAssist (first tab) and the training program for pharmacists (third tab).

Regarding the Educational Component

- The RevAssist program focuses on prevention of pregnancy, however, Revlimid has other serious risks that would be important to convey to the patient, such as neutopenia, thrombocytopenia and infections. The end of the labeling contains information for the patient with an **Authorization** that the patient must sign. We recommend that the other serious risks with Revlimid be included as part of the information conveyed to the patient prior to signing of the Authorization.
- S.T.E.P.S. and RevAssist are not as specific as iPLEDGE concerning appropriate contraceptive methods. For example, the female condom is not an acceptable method in iPLEDGE. The brochure included in the RevAssist patient package If there are methods of birth control that aren't acceptable in RevAssist then this should be stated. One option is to include a table of primary and secondary forms of acceptable birth control similar to the one in the isotretionoin labeling.
- If the prescribing healthcare provider is not properly trained to provide in depth contraceptive counseling, then the sponsor should consider making provisions to ensure appropriate patient referral to a contraceptive counselor prior to starting lenalidomide. Reimbursement for contraceptive counseling services should not be a barrier if such referrrals are necessary.
- The "RevAssist Kit" should not use "planned parenthood brochures" as a surrogate for face-to-face contraceptive counseling of FCBP with an appropriately trained healthcare provider. Written materials alone are neither sufficient nor appropriate for this purpose. A specific provision for face-to-face contraceptive counseling with a medical practitioner ideally should be established as part of the RevAssist program.

There should be brochures concerning the different contraceptive methods provided separately by the counseling healthcare provider.

- In all studies that have investigated contraceptive compliance, unscheduled uterine bleeding has been the leading cause of patient self-discontinuation of hormonal contraceptive methods. Since the majority of effective methods of contraception are hormonal products that depend on the exogenous delivery of estrogen/ progestin to stabilize the endometrium, it would appear that there will be more unscheduled and inappropriate uterine bleeding in the population of women for whom lenalidomide will be prescribed. Since these women will either have underlying thrombocyctopenia or have thrombocytopenia develop as a result of their lenalidomide treatment, they are much more likely to have unscheduled uterine bleeding than a standard non-diseased population of reproductive-aged women. Accordingly, both contraceptive counselors and the written contraceptive materials that are provided to patients should address this issue of unscheduled bleeding specifically in order to insure that women treated with lenalidomide do not inappropriately discontinue their effective birth control methods as a result of unscheduled uterine bleeding.

Regarding the Registration/Distribution Process

- Please verify the number of specialty pharmacies. Will these numbers increase over time?
- What is the expected time delay with a mailed prescription?

Appendix 3. ODS and PLT's Review of Celgene's response letter submitted November 16, 2005 (forwarded by email to DODP on 12-5-05)

ODS has reviewed the responses to comments by the Agency faxed to Celegene on November 9, 2005 on their proposal for a Risk Minimization Action Plan (RiskMAP). We have reviewed Celgene's submission of November 16, 2004, and have the following comments to DODP and/or the Sponsor. These are in **bolded text**.

1. FDA Comment (November 9, 2005)
   We have reviewed the most recent submission of October 6, 2005 and have a number of critical comments and questions that need a sponsor response. In addition to these, we request any sponsor response to our critical questions and comments also include an explicit and detailed side-by-side comparison of RevAssist to S.T.E.P.S.. In our review, we found multiple areas of ambiguity where we could not determine whether RevAssist diverged from current S.T.E.P.S. procedures.

   In addition to these critical comments, we have a number of important comments and questions for which we seek a sponsor response.

   Celgene Response (November 16, 2005)
   As stated in all of our previous correspondence, Celgene has agreed to implement the S.T.E.P.S. ® procedures in its RevAssist℠ program. There is no divergence except for a few enhancements to safety or compliance. These include primarily an additional pregnancy test requirement, 10-14 days before receiving the prescription, and the use of contracted pharmacies.

   Celgene has updated the table previously supplied on September 22, 2005, to include additional details as requested in the November 9 letter (see attached).

- **FDA Comment**

  We conclude that the RevAssist program overall looks comparable to S.T.E.P.S. based on the side-by-side comparison table that Celegene provided and therefore is acceptable to us for interim use until the questionable teratogenicity of lenalidomide is fully characterized and resolved. However, if animal or human teratogenicity is demonstrated, we would suggest the program be modified to reflect state-of-the-art pregnancy prevention risk management standards in pregnancy testing (eg. sensitivity to 25 mIU/mL) and contraceptive technology (e.g. removal of all references to [redacted]), and clear definition of females of child-bearing potential. Currently the standards being implemented for the iPLEDGE program represent the Agency's recommendations of the best available standards). If adeqeuate animal teratogenicity testing is reassuring about fetal risks such that the RevAssist program to prevent pregnancy exposures is discontinued, we

recommend a pregnancy registry be established to monitor for potential human teratogenicity.

2. FDA Comment (November 9, 2005)
The primary goal of the RiskMAP should be to prevent fetal exposures pending complete and adequate preclinical characterization of the teratogenic potential of lenalinoamide.

Celgene Response (November 16, 2005)
Celgene agrees with this statement.

- **FDA Comment**

ODS acknowledges Celgene's Response.

3. FDA Comment (November 9, 2005)
The RiskMAP should be included in final approved labeling.

Celgene Response (November 16, 2005)
Celgene agrees to this statement and included the RiskMAP language in the proposed label currently under review (submitted September 26, 2005).

- **FDA Comment to DOPD**

To ensure that risk management is adequately incorporated into the product label, ODS requests that DODP and ODS jointly review these sections of the label.

4. FDA Comment (November 9, 2005)
All educational materials for patients and providers need to describe the RiskMAP. (We note that the patient brochure, "Getting started with Revlimid" does not mention the need for contraception and pregnancy testing.)

Celgene Response (November 16, 2005)
Celgene agrees that all commercial materials will reflect the final, approved label and the RiskMAP. The brochure cited here was developed prior to the Division's request to implement the current risk management program.

- **FDA Comment to DOPD**

ODS suggests DODP confirm with CDER Office of Regulatory Policy what educational materials must be finalized prior to approval and how those materials should be referenced or included in product labeling. We note that the

iPLEDGE program was recently approved under Subpart H to prevent fetal exposures and that its educational program (actual titles of educational materials) is included as an enclosure in the action letter as well as in the Precautions section of the PI.

5. FDA Comment (November 9, 2005)
The current standard for RiskMAPs of this type includes a Medication Guide.

Celgene Response (November 16, 2006)
Celgene will submit a Medication Guide with the revised proposed labeling for this product.

- **FDA Comment to DODP**

ODS/DSRCS will review and provide comment on Medication Guide submitted November 16, 2005, in a separate letter. Acceptable language to FDA will need to be finalized prior to approval.

6. FDA Comment (November 9, 2005)
The current pregnancy test schedule as proposed by the sponsor is inadequate. Either the pregnancy test schedule of the current S.T.E.P.S. program or the one outlined in the current iPLEDGE program for isotretinoin should be followed.

Celgene Response (November 16, 2005)
Celgene does not understand this comment, as we have proposed the pregnancy testing schedule requested by the FDA representative from the Pregnancy and Lactation Group, a schedule that is more rigorous than the current S.T.E.P.S.® program.

- **FDA Comment**

We agree with the current pregnancy testing schedule. Our original comment was based on the pregnancy testing schedule proposed in the October 27, 2005 version of the proposed label.

7. FDA Comment (November 9, 2005)
Provide clarification on the following items regarding registration/distribution process:
Whether each patient is registered one time and followed longitudinally or whether registration of the patient occurs with each prescription.

Celgene Response (November 16, 2005)

Consistent with S.T.E.P.S.®, in RevAssist℠ the patient registers once in a central system and is followed longitudinally. The registration is inactivated if there is no activity for 12 months (re-registration is then required, before drug can be dispensed).

- **FDA Comment**

This is acceptable.

8. FDA Comment (November 9, 2005)
Provide clarification on the following items regarding registration/distribution process:
How pregnancy test results are communicated to the pharmacist so that the prescription can be filled. Does the existence of an authorization number on the prescription mean that the pregnancy test was negative? Or does obtaining a confirmation number by the pharmacist mean the pregnancy test result was negative?

Celgene Response (November 16, 2005)
Consistent with S.T.E.P.S.®, the pregnancy test results are evaluated by the physician. The physician answers the test result question in the IVR (Interactive Voice Recognition) system and receives an authorization number only if the test result was negative. Therefore, the existence of an authorization number on the prescription means that the pregnancy test was negative. In both S.T.E.P.S.® and RevAssist℠, the physician registration process for obtaining initial and subsequent prescriptions is identical and is described as follows: (description of process for both RiskMAPs was provided in Celgene's response).

- **FDA Comment**

This is acceptable.

9. FDA Comment (November 9, 2005)
Provide clarification on the following items regarding registration/distribution process:
How and where are the results of the pregnancy tests and contraceptive methods used documented, especially for evaluation of the RiskMAP program?

Celgene Response (November 16, 2005)
Consistent with S.T.E.P.S.®, the results of the pregnancy tests and contraceptive methods used are documented in the patient chart.

- **FDA Comment**

This is acceptable.

10. FDA Comment (November 9, 2005)
Provide clarification on the following items regarding registration/distribution process:
How is there assurance that pregnancy testing results will be verified by a physician and appropriately timed?

Celgene Response (November 16, 2006)
See response to question above.

- **FDA Comment**

This is acceptable.

11. FDA Comment (November 9, 2005)
Provide clarification on the following items regarding registration/distribution process:
Are home pregnancy tests acceptable in this program?

Celgene Response
Consistent with S.T.E.P.S. ®, a pregnancy test with a sensitivity of at least 50 mIU/mL performed in a physician's office is acceptable. Also consistent with S.T.E.P.S. ®, a home pregnancy test of appropriate sensitivity, read by someone other than the patient, would be permitted under extraordinary circumstances. "Extraordinary circumstances" is defined as the patient being incapable of going to the physician's office.

- **FDA Comment**

This is minimally acceptable. The current standard is that pregnancy tests have a sensitivity of 25mIU/mL and that pregnancy testing be conducted in a CLIA certified laboratory.

12. FDA Comment (November 9, 2005)
The "7-day window" for dispensing lenalidomide should be linked explicitly to the date of the performance of the last pregnancy test. As currently stated, it is unclear whether and how the most recent pregnancy test is in any way coupled to the date that the prescription for lenalidomide is written and transmitted. The pregnancy test result is the most important aspect of the RiskMAP for assuring that physicians do not prescribe and pharmacists do not dispense lenalidomide to women with an on-going pregnancy.

Celgene Response (November 16, 2005)

In Celgene's experience with S.T.E.P.S.®, the 7-day window, measured from the date of the prescription which is written within 24 hours of a negative pregnancy test, has been effective and does not compromise the integrity of the system. This is the practice to be followed in RevAssist℠. An additional safeguard is that a pregnancy test must be negative both 10-14 days and 24 hours prior to writing the first prescription and within 24 hours prior to writing all subsequent prescriptions.

- **FDA Comment**

This is acceptable for the interim program. If animal or human teratogenicity is found, then our previous comments on page 2 would apply.

13. FDA Comment (November 9, 2005)
Please clarify the prescribing physician's responsibility for contraceptive counseling, monitoring of compliance with birth control methods, and review/ reporting of pregnancy test results and how this will be documented to the RiskMAP program. In addition, please clarify how such participation will be documented and how often this documentation to the RiskMAP program will occur. How does the sponsor plan to monitor compliance with these critical issues?

Celgene Response (November 16, 2005)
Consistent with S.T.E.P.S.®, the physician is responsible for advising the patient of the need for contraception and is expected to refer the patient to an expert for contraceptive counseling if the prescriber is uncomfortable or unable to provide adequate counseling. With each prescription, the physician is asked by the IVR for the pregnancy test results and whether the patient has been compliant with the birth control requirements. The following instructions are provided to the physician with regard to counseling and pregnancy testing (description of Prescriber counseling was provided in Celgene's response).

- **FDA Comment**

This is acceptable, however we note the following counseling requirements in S.T.E.P.S.® that won't be required in the RevAssist℠ program:
  - **Not to extensively handle or open thalidomide**
  - **Thalidomide is present is semen and risk to the fetus from the semen of male patients is unknown.**

ODS is not aware of any reason for these requirements to be applied to lenalidomide and defers to DODP to decide on the need for this counseling to be done.

14. FDA Comment (November 9, 2005)

Will Revlimid ONLY be shipped to the patient by the pharmacist or can the patient go to the pharmacy and have face-to-face counseling, receive the new patient educational materials, and pick up the drug?

Celgene Response (November 16, 2005)
Under no circumstances does a patient receive a prescription without counseling from the contracted pharmacist. The contact will mainly be via the telephone. Prescriptions primarily will be shipped to the patient after counseling. There are certain managed care pharmacies that will be contracted for distribution of REVLIMID. Only pharmacists at these pharmacies will be trained for face-to-face counseling.

All pharmacies authorized to dispense REVLIMID are under a contractual obligation with Celgene to follow the risk management plan. This further ensures that required counseling will take place, and educational materials will be provided, in accordance with requirements of the RevAssist℠ program.

- **FDA Comment**

This is acceptable.

15. FDA Comment
Please clarify what the consultant pharmacist is supposed to do in the event that they determined that the FCBP is not and has not been on appropriate contraception.

Celgene Response
REVLIMID is not to be dispensed; the patient is to be instructed not to take any drug she may still have; and the prescribing physician and Celgene are to be notified.

- **FDA Comment**

This is acceptable as long as these instructions are outlined in contracting pharmacies' Standard Operating Procedures. Celgene is encouraged to think about other scenarios that the consultant pharmacist could face that might require explicit instructions/procedures. Examples might include:
- **Unable to reach patient by telephone to counsel them.**
- **Patient states that pregnancy tests were not conducted.**

16. FDA Comment (November 9, 2005)
We ask to review the physician and patient IVR survey questions for their acceptability.

Celgene Response (November 16, 2005)
Copies of these surveys are provided (see attachment).

- **FDA Comment**

These survey questions appear appropriate and consistent with S.T.E.P.S.® survey questions.

17. FDA Comment (November 9, 2005)
Submit details regarding your evaluation plan; specifically your:
    - Pregnancy Registry Protocol and Pregnancy Exposure Follow-up plan
    - Voluntary Follow-up Survey for patients, physicians, and nurses
    - Quarterly pharmacy audits protocol

Celgene Response (November 16, 2005)
Evaluation of RevAssist℠ will be similar to current practices regarding ongoing evaluation of S.T.E.P.S.® Celgene commits to provide copies of these documents when they have been finalized, after availability of the final product label.

- **FDA Comment**

ODS asks that Celgene to develop a clear pregnancy exposure follow-up plan consistent with the S.T.E.P.S. program prior to approval.). If adeqeuate animal teratogenicity testing is reassuring about fetal risks such that the RevAssist program to prevent pregnancy exposures is discontinued, we recommend a pregnancy registry be established to monitor for potential human teratogenicity Other components of the evaluation plan (Voluntary Follow-up survey and Quarterly pharmacy audits) should be submitted within 6 months following product approval. ODS also asks that the company specifically describe how they will monitor the contracted pharmacies' performance of the necessary risk management procedures, since the use of such pharmacies is different from S.T.E.P.S..

18. FDA Comment (November 9, 2005)
The occurrence of pregnancy exposures should be viewed as a serious adverse event. FDA should be notified of all exposed pregnancies within 15 days of receipt of information by Celgene.

Celgene Response (November 16, 2005)
Consistent with S.T.E.P.S.®, Celgene will notify FDA of all exposed pregnancies within 24-28 hours via telephone or facsimile and in writing within 15 days of receipt of the information by Celgene. To date, Celgene has notified the FDA the same day via telephone or facsimile of any female of child bearing potential who may have had a positive pregnancy test while taking THALOMID.

- **FDA Comment**

This is acceptable.

19. FDA Comment (November 9, 2005)
The issue of which patients should be considered "adult females not of childbearing potential" has not been adequately addressed in the Revlimid RiskMAP or the educational materials. A definition of women who fall into this category is required. Definitions that would be acceptable and consistent with the current iPLEDGE program are as follows:

> All adult women are considered females of childbearing potential (FCBP) if they have NOT previously been documented to have either:
>
> > (A) a hysterectomy or
> > (B) menopause
>
> Menopause is assumed to have occurred in a woman when there is either:
>
> > (a) appropriate medical documentation of prior complete bilateral oophorectomy (i.e., surgical removal of the ovaries, resulting in "surgical menopause"), or
> >
> > (b) permanent cessation of previously occurring menses as a result of ovarian failure with documentation of hormonal deficiency* by a certified healthcare provider (i.e., "spontaneous menopause", which occurs in the United States at a mean age of 51.5 years).
>
> *Hormonal deficiency should be appropriately documented in the case of suspected spontaneous menopause as follows:
>
> (1) If age >54 years and with the absence of normal menses: Serum FSH (Follicle Stimulating Hormone) level elevated to within the post-menopausal range based on the laboratory reference range where the hormonal assay is performed;
>
> (2) If age <54 years and with the absence of normal menses: Negative serum or urine β-HCG with concurrently elevated serum FSH (Follicle Stimulating Hormone) level in the post-menopausal range, depressed estradiol (E_2) level in the post-menopausal range, and absent serum progesterone level, based on the laboratory reference ranges where the hormonal assays are performed.

Celgene Response (November 16, 2005)
As in S.T.E.P.S.®, the following definitions are used in RevAssist℠:

- Females not of childbearing potential include females who have had a natural menopause for at least 24 consecutive months, a hysterectomy, and/or bilateral oophorectomy.

- Females of childbearing potential are all other females who are menstruating, amenorrheic from previous medical treatments, under 50 years of age, and/or perimenopausal.

- **FDA Comment**

  This is acceptable for the interim program. If animal or human teratogenicity is demonstrated for lenalidomide, the definition of FCBP will need to be modified to bring it up to current standards (as described in our original comment on page 2).

20. FDA Comment (November 9, 2005)
    Please completely describe the Revlimid RiskMAP in the text of the documentation. References to the labeling and brochures may be included in the text.

    Celegene Response (November 16, 2005)
    Once all aspects of the program have been agreed, Celgene commits to modify the RiskMAP document as needed to ensure it is consistent with all Agency requirements.

- **FDA Comment**

  This is acceptable. Please consult ODS on making sure this documentation is adequate, including the contents of the Medication Guide.

21. FDA Comment (November 9, 2005)
    Please make all portions of the RiskMAP document consistent. For example, there are discrepancies between the overall description of RevAssist (first tab) and the training program for pharmacists (third tab).

    Celegene Response (November 16, 2005)
    Once all aspects of the program have been agreed, Celgene commits to modify the RiskMAP document as needed to ensure it is consistent with all Agency requirements.

- **FDA Comment**

  This is acceptable.

22. FDA Comment (November 9, 2005)
    The RevAssist program focuses on prevention of pregnancy, however, Revlimid has other serious risks that would be important to convey to the patient, such as

neutropenia, thrombocytopenia and infections. The end of the labeling contains information for the patient with an Authorization that the patient must sign. We recommend that the other serious risks with Revlimid be included as part of the information conveyed to the patient prior to signing of the Authorization.

Celegene Response (November 16, 2005)
Consistent with S.T.E.P.S.®, the authorization at the end of the package insert is NOT the document signed by the patient. The document signed by the patient is the Physician Patient Agreement Form (submitted as Tab 4 of the October 6, 2005 submission).

- **FDA Comment**

Explain what the authorization form is for and why it is different from the Physician-Patient Agreement Form. We strongly recommend the Physician-Patient Agreement Form include or reference the medication guide or other source of complete safety information.

23. FDA Comment (November 9, 2005)
S.T.E.P.S. and RevAssist are not as specific as iPLEDGE concerning appropriate contraceptive methods. For example, the female condom is not an acceptable method in iPLEDGE. The brochure included in the RevAssist patient package [redacted]. If there are methods of birth control that aren't acceptable in RevAssist then this should be stated. One option is to include a table of primary and secondary forms of acceptable birth control similar to the one in the isotretionoin labeling.

Celegene Response (November 16, 2005)
Consistent with S.T.E.P.S.®, the proposed label currently under review (submitted September 26, 2005) contains a list of acceptable birth control methods.

- **FDA Comment**

This is acceptable for the interim program, if animal or human teratogenic data are demonstrated, contraceptive educational materials will need to be modified to assure that patients and clinicians are informed about acceptably effective contraceptive practices.

24. FDA Comment (November 9, 2005)
If the prescribing healthcare provider is not properly trained to provide in depth contraceptive counseling, then the sponsor should consider making provisions to ensure appropriate patient referral to a contraceptive counselor prior to starting lenalidomide. Reimbursement for contraceptive counseling services should not be a barrier if such referrals are necessary.

Celegene Response (November 16, 2005)
As in S.T.E.P.S. ®, Celgene will assure that reimbursement is not a barrier to contraceptive counseling.

- **FDA Comment**

This is acceptable.

25. FDA Comment (November 9 ,2005)
The "RevAssist Kit" should not use "planned parenthood brochures" as a surrogate for face-to-face contraceptive counseling of FCBP with an appropriately trained healthcare provider. Written materials alone are neither sufficient nor appropriate for this purpose. A specific provision for face-to-face contraceptive counseling with a medical practitioner ideally should be established as part of the RevAssist program. There should be brochures concerning the different contraceptive methods provided separately by the counseling healthcare provider.

Celegene Response (November 16, 2005)
Consistent with S.T.E.P.S. ®, the planned parenthood brochure is not a surrogate. It is provided in the kit as a tool for the physician to use, should the physician choose to do so.

- **FDA Comment**

ODS and PLT recommend the company clarify to the prescribing physician and to patients that are being counseled that if the planned parenthood brochure differs from the contraceptive methods recommended in the labeling, the labeling recommendations supersede recommendations in the planned parenthood brochure.

26. FDA Comment (November 9, 2005)
In all studies that have investigated contraceptive compliance, unscheduled uterine bleeding has been the leading cause of patient self-discontinuation of hormonal contraceptive methods. Since the majority of effective methods of contraception are hormonal products that depend on the exogenous delivery of estrogen/ progestin to stabilize the endometrium, it would appear that there will be more unscheduled and inappropriate uterine bleeding in the population of women for whom lenalidomide will be prescribed. Since these women will either have underlying thrombocyctopenia or have thrombocytopenia develop as a result of their lenalidomide treatment, they are much more likely to have unscheduled uterine bleeding than a standard non-diseased population of reproductive-aged women. Accordingly, both contraceptive counselors and the written contraceptive materials

that are provided to patients should address this issue of unscheduled bleeding specifically in order to insure that women treated with lenalidomide do not inappropriately discontinue their effective birth control methods as a result of unscheduled uterine bleeding.

Celegene Response (November 16, 2005)
Consistent with S.T.E.P.S.®, patients who have irregular menses will have more frequent pregnancy tests (see question above). Additionally, the written materials to be provided will specify that birth control is to be used continuously, including during periods of treatment interruption, or unscheduled bleeding.

- **FDA Comment**

This is acceptable.

27. FDA Comment (November 9, 2005)
Please verify the number of specialty pharmacies. Will these numbers increase over time?

Celegene Response (November 16, 2005)
Celgene is currently planning to execute contracts with — national specialty pharmacies, and some Managed Care Pharmacies. The number is expected to change over time based on compliance with the RevAssist program, patient volume, geographic coverage, or other needs.

- **FDA Comment**

This is acceptable.

28. FDA Comment (November 9, 2005)
What is the expected time delay with a mailed prescription?

Celegene Response (November 16, 2005)
Prescriptions will be shipped for overnight delivery (1 – 2 days).

- **FDA Comment**

This is acceptable.

ODS Reviewers
Jeanine Best, M.S.N., R.N., P.N.P., Patient Product Information Specialist, DSRCS
Nancy Clark, PharmD, Project Manager, DSRCS
Mary Dempsey, Project Management Officer, ODS IO
Claudia Karwoski, PharmD, Scientific Coordinator, ODS IO
Susan Lu, RPh, Safety Evaluator Team Leader, DDRE
Carolyn McCloskey, M.D., M.P.H., Epidemiologist, DDRE
Toni Piazza-Hepp, PharmD, Deputy Director, DSCRS
Mary Willy, Ph.D., Epidemiology Team Leader, DDRE

Concurrence:
Mark Avigan, MD, CM, Director, DDRE, HFD-430
Gerald DalPan, MD, MHS, Director, DSRCS, HFD- 410

PLT Reviewers
Kathleen Uhl, M.D., Medical Team Leader
Gerry Nahum, M.D., Medical Officer
Dianne Kennedy, RPh, M.P.H., Program Manager

_____
Anne Trontell, M.D., M.P.H., Deputy Director
Office of Drug Safety, HFD-400

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/s/

Mary Dempsey
12/15/2005 09:01:30 AM
DRUG SAFETY OFFICE REVIEWER

Anne Trontell
12/15/2005 02:49:29 PM
DRUG SAFETY OFFICE REVIEWER

MEMO

To: Robert Justice, MD
Acting Director, Division of Drug Oncology Products
HFD-150

From: Kimberly Pedersen, RPh
Safety Evaluator, Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

Through: Alina Mahmud, RPh, MS, Team Leader
Denise P. Toyer, PharmD, Deputy Director
Carol A. Holquist, RPh, Director
Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

Date: December 14, 2005

Re: ODS Consult 03-0271-3, Revlimid (Lenalidomide) Capsules 5 mg and 10 mg; NDA 21-880

This memorandum is in response to a December 8, 2005 request from your Division for a re-review of the proprietary name, Revlimid. The container label, carton, and insert labeling were provided for review and comment.

Since our initial review dated March 2003 (ODS consult 03-0271) and second review dated June 2, 2005 (ODS consult 03-0271-1) DMETS has not identified any additional proprietary names as having potential sound-alike and look-alike characteristics with Revlimid that would render the name objectionable. DDMAC found the proprietary name of Revlimid acceptable from a promotional perspective in both the initial review and this re-review.

Upon review of the proposed labels and labeling, DMETS has identified the following areas of possible improvement, which may minimize potential user error.

A. Container Label:

1. In the current presentation, the two different strengths are the same color, which increases the potential of selection errors. Differentiate the two products strengths (5 and 10 mg) by the addition of color, blocking, boxing or other means, in order to reduce potential confusion.

2. Revise the font of the established name and dosage form to assure the presentation is identical. Currently, "capsules" is presented in a smaller font.

3. Relocate the net quantity statement away from the product strength to another less prominent location on the principal display panel. The close proximity of the two numbers could result in confusion and/or error.

4. Assure child resistant closures are used for bottles intended to be a "unit of use" (e.g. 30 capsule size) to be in accordance with the Poison Prevention Act.

B. Insert Labeling

1. General Comment

Thalomid AERS cases were reviewed for medication errors as the proposed drug product of Revlimid is chemically similar with the same sponsor and ordering system. In this review, twenty-two reports of pregnancy or potential pregnancy in a partner of a male receiving Thalomid were found. Of note, many of these were poorly documented and may not conclusively involve pregnancy post-therapy with Thalomid. However, DMETS questions if warnings to the sexually active male patients should also include suggestions that the partner use a reliable method of contraception (in addition to the patient's use of a condom).

2. Dosage and Administration

a. We recommend the addition of the second paragraph from "geriatric use" section of "Precautions", which refers to care in dose selection and renal monitoring in patients renal function.

b. We recommend the addition of the statement (from the Medication Guide), "Do not break, chew, or open" the capsules. This section of the package insert often serves as the reference for practitioners and this information is pertinent to proper administration. For an example for what can occur when Revlimid is introduced into the marketplace, a Thalomid post-marketing report noted that a pregnant practitioner opened the capsules and was exposed to the medication.

c. We recommend the addition of "with water" (from the Medication Guide) to the initial sentence of this section; thus, the sentence would read:

"The recommended starting dose of Revlimid (lenalidomide) is 10 mg with water daily. Dosing is continued or modified based upon clinical and laboratory findings."

d. The laboratory values presented to help evaluate dosage adjustments are cited with the greek presentation of micro (µ). Revise to the more acceptable "mcL" presentation, since "µl" may be confused with "mL" (milliliter). The USP Quality Review[1] includes "µg" on their list of potentially dangerous abbreviations for the same reasoning.

In summary, DMETS has no objection to the use of the proprietary name of Revlimid from a safety perspective. In addition, DMETS recommends implementation of the label and labeling revisions outlined in this memo to minimize potential errors with the use of this product. DDMAC found the proprietary name of Revlimid acceptable from a promotional perspective in both the initial review and this re-review. This is considered a final decision. However, if the approval of the NDA is delayed beyond 90 days from the signature date of this document, the name with its associated labels and labeling must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and/or established names from the signature date of this document.

We would be willing to meet with the Division for further discussion if needed. If you have any questions or need clarification, please contact Diane Smith at 301-726-0538.

[1] USP Quality Review, Number 80, Issued on July 2004. Potentially Dangerous Abbreviations. WWW.USP.ORG/PATIENTSAFETY/NEWSLETTERS/QUALITYREVIEW/QR802004-07-01B.html.

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/s/

Kimberly Culley-Pedersen
12/20/2005 03:25:06 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
12/20/2005 03:32:36 PM
DRUG SAFETY OFFICE REVIEWER

Celgene Corporation
86 Morris Avenue
Summit, New Jersey 07901
Tel 908-673-9000
Fax 908-673-9001

December 9, 2005

Robert Justice, M.D.
Acting Director, Division of Oncology Drug Products
Center for Drug Evaluation and Research / HFD-150
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705

NDA 21-880
REVLIMID® (lenalidomide)

ORIGINAL AMENDMENT
N(BL)

RE: LABELING COMMENTS

Dear Dr. Justice:

On December 8, 2005, Celgene Corporation (Celgene) received comments from FDA regarding the REVLIMID® label and Medication Guide. Celgene has reviewed these comments and agrees to the proposed modifications. Copies of the revised label and revised redlined label are provided.

The revised label also contains a correction to the Sponsor telephone number from 1-888-4CELGENE to 1-888-4CELGEN. Additionally, we have made a slight change for clarity regarding the type of MDS indicated for treatment in line 711; and we have added information on what the patient should do if a dose is missed (lines 749-751), as requested. The changes are highlighted in the redlined version of the label.

Celgene would accept this proposed label as a final label. It includes a comprehensive, robust, proven controlled-distribution system that will effectively address public safety interests.

Celgene is committed to work expeditiously with the Agency on any further changes that may be needed in the future, based on ongoing research and marketing experience.

If you have any questions about this document or need further information, please contact me by telephone at (908) 673-9551, by facsimile at (908) 673-2763, or by email at gtoolan@celgene.com.

Sincerely,

Gretchen Toolan
Director, Regulatory Affairs
GT/es

56 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(5) Draft Labeling

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

RECEIVED

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Celgene Corporation	December 9, 2005 DEC 14 2005
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)* CDER White Oak DR1
(908) 673-9000	(908) 673-2763
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE RECEIVED
86 Morris Avenue Summit, NJ 07901	Not Applicable DEC 13 2005

PRODUCT DESCRIPTION

CDER/CDER

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-880

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Lenalidomide	REVLIMID®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
3-(4'amino-1,3-dihydro-1-oxo-2H-isoindol-2-yl)-2,6-piperidinedione	CC-5013,CDC-501,Imid 1, Imid 2, CI-B, Compound 8a, Revimid

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Capsule	5 and 10 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

REVLIMID ® is indicated for the treatment of patients with transfusion-dependent anemia due to low- or intermediate –1- risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Response to FDA Request for Information

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

N/A

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)
IND numbers: 60,100,
DMF Numbers:

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☒	2. Labeling *(check one)* ☒ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER: Response to FDA Request for Information

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

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

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
	Gretchen Toolan, Director, Regulatory Affairs	December 9, 2005
ADDRESS *(Street, City, State, and ZIP Code)*		Telephone Number
86 Morris Avenue, Summit, New Jersey 07901		(908) 673-9551

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
1401 Rockville Pike
ockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 7, 2005

TO: Robert Justice, M.D., Director
Division of Oncology Drug Products

VIA: Carl Huntley, R. Ph., MBA, Regulatory Project Manager
Division of Oncology Drug Products

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support

THROUGH: Toni Piazza-Hepp, Pharm.D., Acting Director
Division of Surveillance, Research, and Communication Support

SUBJECT: DSRCS Review of Medication Guide for Revlimid (lenalidomide), NDA 21-880

Background and Summary

The following are our recommended revisions for the Medication Guide for Revlimid (lenalidomide), NDA 21-880. We have simplified the wording, made it consistent with the PI, removed unnecessary information, and put it in the format specified for Medication Guides in 21 CFR 208.20. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

These revisions are based on draft labeling submitted by the sponsor on November 30, 2005. Medication Guides should always be consistent with the prescribing information. All future relevant changes to the PI should also be reflected in the Medication Guide.

Comments and Recommendations

We also have the following comment:

1. Per 21 CFR 201.57(f)(2): "Any printed patient information or Medication Guide required under this chapter to be distributed to the patient shall be referred to under the "Precautions" section [information for Patients subsection] of the labeling and the full text of such patient information or Medication Guide shall be reprinted at the end of the labeling." The sponsor needs to adhere to this regulation.

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___ § 552(b)(5) Deliberative Process

__/ § 552(b)(5) Draft Labeling

10 Page(s) Withheld

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✓ § 552(b)(5) Deliberative Process

___ § 552(b)(5) Draft Labeling

CELGENE CORPORATION
Regulatory Affairs
86 Morris Avenue
Summit, NJ 07901

FAX TRANSMISSION SHEET
FAX NO: 908-673-2762

TO:	Carl Huntley
COMPANY:	FDA
FAX NO:	301-796-9845
NUMBER OF PAGES (Including Cover Sheet):	31
DATE:	November 30, 2005
FROM:	Gretchen Toolan
TELEPHONE:	908-673-9551

If there are any problems, please call 908-673-9253

The following is Celgene's response to FDA's label comments of November 23.

36 Page(s) Withheld

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___ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Celgene Corporation
86 Morris Avenue
Summit, New Jersey 07901
Tel 908-673-9000
Fax 908-673-9001

November 30, 2005

Robert Justice, M.D.
Acting Director, Division of Oncology Drug Products
Center for Drug Evaluation and Research / HFD-150
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705

NDA 21-880
REVLIMID® (lenalidomide)

RE: LABELING COMMENTS

Dear Dr. Justice:

On November 23, 2005, Celgene Corporation (Celgene) received comments from FDA regarding the REVLIMID® label. Celgene has reviewed these comments and agrees to the majority of the proposed modifications. A copy of the revised label is provided.

However, we would like to further discuss one point. If at all possible, we would appreciate your scheduling a short telephone conversation to discuss this point. Celgene believes that we are close to a final label and a conversation would help resolve this outstanding issue.

1. As stated previously, the — — Thus, we believe it should be mentioned in the label. Celgene proposes the following wording based on the ITT analysis and consistent with a facsimile from Celgene sent to FDA on August 23, 2005 in response to the FDA request for information dated August 10, 2005:

   This — is consistent with data presented at ODAC in the Agency review.

   While not included within the original MDS-003 study protocol, the final statistical analysis plan for this study specified the modification to the IWG criteria that were used for the definition of transfusion independence. The modified criteria, as used in our NDA, —

If you have any questions about this document or need further information, please contact me by telephone at (908) 673-9551, by facsimile at (908) 673-2763, or by email at gtoolan@celgene.com.

Sincerely,

Gretchen Toolan
Director, Regulatory Affairs

GT/es

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Celgene Corporation	November 30, 2005
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(908) 673-9000	(908) 673-2763
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE**
86 Morris Avenue Summit, NJ 07901	Not Applicable

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21 -880

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Lenalidomide	REVLIMID®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
3-(4'amino-1,3-dihydro-1-oxo-2H-isoindol-2-yl)-2,6-piperidinedione

CODE NAME *(If any)*
CC-5013,CDC-501,Imid 1, Imid 2, CI-B, Compound 8a, Revimid

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Capsule	5 and 10 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
REVLIMID ® is indicated for the treatment of patients with transfusion-dependent anemia due to low- or intermediate –1- risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Labeling Comments

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

N/A

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)
IND numbers: 60,100, —
DMF Numbers: —

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER:

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

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

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Gretchen Toolan	Gretchen Toolan, Director, Regulatory Affairs	November 30, 2005

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
86 Morris Avenue, Summit, New Jersey 07901	(908) 673-9551

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

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MEMORANDUM OF MEETING MINUTES

MEETING DATE:	August 23, 2005
TIME:	1:00 PM
LOCATION:	Room G, WOCII
APPLICATION:	NDA 21-880
DRUG NAME:	Revlimid (lenalidomide, CC-5013)
TYPE OF MEETING:	Type A, Risk Minimization plan for Revlimid

MEETING CHAIR: Dr. Maitreyee Hazarika

MEETING RECORDER: CAPT Carl Huntley

FDA ATTENDEES:

Robert Justice, M.D., Acting Director
Ann Farrell, M.D., Medical Team Leader
Maitreyee Hazarika, M.D., Medical Officer
Edvardas Kaminskas, M.D. Medical Officer
John Leighton, Ph. D., Pharmacology Team Leader
Anwar Goheer, Ph. D., Pharmacology Reviewer
Kimberly Benson, Ph. D., Pharmacology Reviewer (reprotox)
Min Chen, Ph. D., Office of Drug Safety
Susan Lu, Ph. D., Office of Drug Safety
Gerard G. Nahum, M.D., Pregnancy and Lactation Team, FDA
Carl Huntley, R. Ph., MBA, Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Dr. Sol Barer	President and Chief Operating Officer
Dr. Graham Burton	Sr. VP, Regulatory Affairs, Global Pharmacovigilance and Project Management
Dr. Robert DeLap	VP, Global Medical Research
Ms. Jayne Butler	Director, Marketing
—	Consultant, —
Dr. Herbert Faleck	VP, Clinical Research and Development
Dr. Louise Latriano	Sr. Director, Toxicology
Dr. David Stirling	Chief Scientific Officer
Mr. Mark Alles	VP, Sales and Marketing
Mr. Larry Pflum	Senior Director, Project Management
Dr. Jerome Zeldis	VP, Medical Affairs and Chief Medical Officer
Ms. Gretchen Toolan	Director, Regulatory Affairs

BACKGROUND:

Celgene is developing lenalidomide, a thalidomide analogue, for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenic abnormality with or without additional cytogenectic

abnormalities. Celgene is also developing Revlimid for the treatment of patients with multiple myeloma. Celgene requested a Type A meeting to discuss their proposed Risk Minimization Plan that would be instituted if Revlimid was approved.

The NDA submitted risk minimization plan consisted of 2 objectives: manage the cytopenia adverse events and reduce the risk of fetal exposure in females of child bearing potential. The sponsor proposes managing the cytopenias through the recommendation of weekly hematologic monitoring for the first 8 weeks with monthly monitoring after that. The management guidance will be included in the package insert, a medication guide, and additional educational materials.

The sponsor plans to provide information in the package insert and medication guide information regarding the benefits and potential risks of taking Revlimid during pregnancy. The sponsor proposes [redacted] for the labeling.

The sponsor's risk management program for physicians includes a package insert, physician information brochure, Physician Frequently Asked Questions, Dosing Pocket Card, education program, and a side-effect management brochure. The sponsor's risk management program for patients includes medication guide, starter kit, blood count information sheet, and patient guide to transfusions, iron overload, and cytopenias. The sponsor's risk management program for nurses includes the package insert, nurse information brochure, education program, and patient information nurse training tool.

MEETING OBJECTIVES:

To discuss Celgene's Risk Minimization Plan.

Meeting Summary
The meeting opened with introductions. A sign-in sheet was distributed.

Celgene presented a brief presentation including a revision of their previously submitted Risk Minimization Plan. The latest version includes the establishment of specialty pharmacies. Celgene stated that they are developing several thalidomide analogues. Revlimid is one of these analogues. Celgene believes that structural similarity does not mean that Revlimid should have the same potential for teratogenicity as thalidomide. Celgene discussed that small changes in the structure between lenalidomide and thalidomide result in differences between the two compounds for efficacy and toxicity.

The Agency communicated that the pharmacology/toxicology review team do not find the developmental toxicity study to be adequate. Therefore, no conclusion can be drawn from the submitted study.

Celgene reported that another developmental toxicity study was underway and they anticipate having the study results in October after the Agency's decision.

Points considered/discussed:

1. Issue of structural similarity/dissimilarity between lenalidomide and thalidomide.

2. Minimization of fetal exposure is the central issue for risk minimization since hematologist/oncologists would be familiar with the management of potential neutropenias.
3. Discussion of ICH maternal dose guidelines and the lowering of the dose in the second rabbit study. (This issue is a mute point until the dose finding study is completely analyzed). The rabbit study is not definitive and the rat study is not adequate. The toxicology team does not have the necessary data to review. Discussion followed as to the literature and use of available animal models.
4. What will be the confirmative developmental study? The toxicity consultant [redacted] makes an argument for the rat study). A primate study would be difficult/not feasible due to spontaneous abortions. FDA suggested a study of the blood in pregnant rabbits (look at cytopenias, etc.)
5. FDA felt that the pregnancy class would be [redacted]
6. FDA discussed the use of a pregnancy registry.
7. The RevAssist program was explained to the agency. This program, while not as expansive as the S.T.E.P.S. program, will be developed to provide the needed information to health care providers (for the management of potential neutropenias and hrombocytopenia and minimization of fetal exposure). Although not finalized, Celgene plans to limit the distribution of REVLIMID® through multiple specialty pharmacies. Specialty pharmacies focus on products that treat patient populations with complex diseases like MDS that require pharmacists with a high level of expertise to educate patients and assist them with their disease management. They have dedicated pharmacists, nurses, and social workers to assist physicians and patients with compliance, counseling, educational materials, and medication delivery. The contract between Celgene and the specialty pharmacies will require them to contact patients who have been prescribed REVLIMID® prior to shipping the prescription. During this phone contact, patients will be educated again on the signs and symptoms of cytopenias, the need for routine blood tests, and the unknown potential risk of exposure to a human fetus. The consultant pharmacists will not ship REVLIMID® to a patient unless they have completed this additional patient counseling. Consultant pharmacists will repeat counseling for patients who receive additional or refilled REVLIMID® prescriptions. In addition, the consultant pharmacist will confirm that the patient understands the risks of REVLIMID® therapy. Again, additional details will be discussed at a later time with the agency regarding the specialty pharmacies.

The meeting was adjourned at 3:00 PM

Submitted by:

_____
Carl Huntley, R.Ph., MBA
Regulatory Project Manager

Concurrence:

_____
Ann Farrell, MD
Clinical Team Leader

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

/s/

Ann Farrell
10/25/2005 03:35:57 PM

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I

DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 827-1539 FAX: (301) 594-0499

TO: Gretchen Toolan
Director, Regulatory Affairs
FAX: (908) 673-2763

FROM: Carl Huntley, R.Ph., MBA
PHONE: (301) 827-1539

Total number of pages, including cover sheet: 2

Date: August 18, 2005

Re: NDA 21-880, Meeting request to discuss your proposed risk minimization plans (RiskMAP) **for Revlimid. Type A Meeting Request - Granted.**

COMMENTS: This is in response to your August 12, 2005 request to discuss your plans with the agency for the proposed risk minimization plans that would be instituted upon approval of REVLIMID in the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.
We have a tentative date of Tuesday, August 23, 2005 at 1:00 to 3:00 PM here at WOCII, 1451 Rockville Pike, Rockville, MD. We received your proposed plan and have planned an internal meeting for August 22, 2005. If you have additional information, please forward to me for the

team to review. I have attached the list of *tentative* FDA invitees for the meeting: A few of the invitees may be joining us via telephone.

FDA Invitees:

Robert Justice, M.D., Deputy Dir.
Ann Farrell, M.D., Medical Team Leader
Maitreyee Hazarika, M.D., Medical Officer
Edvartas Kaminskas, M.D., Medical Reviewer, Safety
John Leighton, Ph..D., Pharmacology Team Leader
Anwar Goheer, Ph.D., Pharmacology Reviewer
Hari Sarker, Ph. D., Chemistry Reviewer
Raji Sridhara, Ph.D., Statistical Team Leader
Yuan Li Shen, Ph. D. Statistician
Brian Booth, Ph. D., ClinPharm Team Leader
Gene Williams, Ph. D. ClinPharm Reviewer
David Jacobson-Kram, Ph. D., Senior Scientist
Kathleen Uhl, M.D., OND
Susan Lu, Pharm. D., ODS
Mary Dempsey, ODS
Joe Grillo, Pharm. D., DDMAC
Carl Huntley, R. Ph., MBA, Regulatory Project Manager

Thanks
-carl

AGENDA
TEAM MEETING

NDA: 21-880: Revlimid (lenalidomide) Capsules: 5 mg and 10 mg

SPONSOR: Celgene

DATE: August 11, 2005 **TIME:** 1:00 PM in Conf B

MEETING PURPOSE: Team meeting to discuss the status of each discipline as needed for this NDA.

FDA Invited ATTENDEES: (primary review team)

Dr. Richard Pazdur	Office Director
Dr. Robert Justice	Actg Division Director
Dr. Ann Farrell	Medical Team Leader
Dr. Maitreyee Hazarika	Medical Reviewer
Dr. Edvardas Kaminskas	Safety Reviewer
Dr. John Leighton	Pharmacology Team Leader
Dr. Anwar Goheer	Pharmacology Reviewer
Dr. Kimberly Benson	Pharmacology, repro Reviewer
Dr. Nallaperumal Chidambaram	Chemistry Team Leader
Dr. Hari Sarker	Chemistry Reviewer
Dr. Raji Sridhara	Statistical Team Leader
Dr. Yuan Li Shen	Statistical Reviewer
Dr. Brian Booth	Clinical Pharmacology Team Leader
Dr. Gene Williams	Clinical Pharmacology Reviewer
CAPT Carl Huntley	Project Manager

MEETING TOPICS :

1. General

May 26, 2005 filing meeting held. This NDA was deemed as file-able. The submission received priority review status bringing the PDUFA date to October 7, 2005. ODAC scheduled for September 14th (AM).
Fast Track Granted April 11, 2003
Orphan Drug Status Granted January 29, 2004 (Transfusion dependent MDS)
Under CFR 314.55 (d) – not required to submit peds data (since Orphan Drug)
Celegene expects to be granted 7 years marketing exclusivity under Section 527 (a)(3) of the Act.
DMETS – had no objection to the use of Revlimid (December 19, 2003)
Presentation by sponsor July 21, 2005

2. Potential Review Problems:

- MEDICAL: *There are still some issues concerning data for transfused patients. Issues are being clarified with sponsor.*
- STATISTICAL: *Being reviewed. Of note: this review will consist of a team comprised of Drs. Ed Kaminskas, Yuan Li Shen, and Maitreyee Hazarika (lead).*
- PHARMACOLOGY/TOXICOLOGY:
- CLIN PHARM/BIOPHARMACEUTICS: *Is 'okay' thus far. Most likely a renal study will be a phase 4 commitment.*
- CMC: *is 'okay'.*

Status of EA - *already submitted.*

Inspection status -

3. Identify Consults, etc:

DDMAC, DSI, ODS – done
Micro not needed.
REPRO ?

Other issues

DSI: -

EER -

Trademark –

Biometrics -

Biopharm (Dissolution) -

Microbiology – not needed

4. ODAC:

Sept 14th, 2005
Practices scheduled for 8/30/05, 9/6/05, 9/8/05 and Monday morning meetings.

5. Action & Goal Dates:

Priority review 10/7/05
Filing date : 6/6/05
Filing Granted Letter (74 day letter): 6/20/05
CSO Filing Review & Minutes (due 30 days after filing: 7/6/05)
Division Goal Date (Action Package completed) – 9/23/05
Action Performance Goal Date (letter signed) -

6. Other Issues:

Risk management plan to be received by the agency on August 12, 2005.

A labeling review will be scheduled at the next meeting.

7. Subsequent Meetings

	DATE	DAY	TIME	ROOM	MEETING TYPE
a.	8/17/05	Wed	1:30 PM	B	Labeling
b.	8/25/05	Thurs	9:30 AM	A	Labeling
c.					
d.					
e.					
f.					
g					

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-880

6/17/05

Celgene Corporation
86 Morris Avenue
Summit, New Jersey 07901

Attention: Gretchen Toolan
Director, Regulatory Affairs

Dear Ms. Toolan:

Please refer to your April 7, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Revlimid Revlimid (lenalidomide), 5 and 10 mg capsules.

We also refer to your submission dated June 1, 2005.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on June 6, 2005 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Carl Huntley, Regulatory Project Manager, at (301) 827-1539.

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/

Dotti Pease
6/17/05 12:05:31 PM
Signing for Richard Pazdur, M.D.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-880

6/17/05

Celgene Corporation
86 Morris Avenue
Summit, New Jersey 07901

Attention: Gretchen Toolan
Director, Regulatory Affairs

Dear Ms. Toolan:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Revlimid (lenalidomide), capsules, 5 and 10 mg

Review Priority Classification: Priority (P)

Date of Application: April 7, 2005

Date of Receipt: April 11, 2005

Our Reference Number: NDA 21-880

Please note that your application was filed on June 6, 2005 in accordance with 21 CFR 314.101(a). The user fee goal date will be October 7, 2005.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. The requirement to submit pediatric data does not apply to any drug for an indication or indications for which orphan drug designation has

been granted (Code of Federal Regulations, (CFR) 314.55(d). We are waiving the requirement for pediatric studies for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic or mixed electronic and paper submissions to the Central Document Room at the following address:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products, HFD-150
Attention: Division Document Room, 3067
5600 Fishers Lane
Rockville, Maryland 20857

If your submission only contains paper, send it to one of the following address:

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products, HFD-150
Attention: Division Document Room, 3067
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, call Carl Huntley, Regulatory Project Manager, at (301) 827-1539.

Sincerely,

{See appended electronic signature page}

Dotti Pease
Chief, Project Management Staff
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/

Carl Huntley
6/17/05 12:18:11 PM
Signing for Dotti Pease

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Office of Drug Safety

MEMO

To: Richard Pazdur, MD
Director, Division of Oncology Products
HFD-150

From: Kimberly Culley, RPh
Safety Evaluator, Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

Through: Alina Mahmud, RPh, MS, Team Leader
Denise P. Toyer, Pharm.D., Deputy Director
Carol A. Holquist, R.Ph., Director
Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

Date: June 2, 2005

Re: ODS Consult 03-0271-2, Revlimid (Lenalidomide) Capsules 5 mg and 10 mg; NDA 21-880

This memorandum is in response to a May 6, 2005 request from your Division for a re-review of the proprietary name, Revlimid. The container label, carton, and insert labeling were provided for review and comment.

Since our initial review dated March 2003 (ODS consult 03-0271), DMETS has not identified any additional proprietary names as having potential sound-alike and look-alike characteristics with Revlimid that would render the name objectionable. DDMAC found the proprietary name of Revlimid acceptable from a promotional perspective in both the initial review and this re-review.

Upon review of the proposed labels and labeling, DMETS has identified several areas of possible improvement, which may minimize potential user error.

A. Container Label:

1. Differentiate the two products strengths (5 and 10 mg) by the addition of color, blocking or other means, in order to reduce potential confusion. In the current presentation, the two different strengths are the same color, which increases the potential of selection errors.

2. Revise the font of the established name and dosage format to assure the presentation is identical. Currently, "capsules" is presented in a smaller font. Additionally, the presentation of the established name and dosage form lacks prominence in comparison to the proprietary name.

3. Relocate the net quantity statement away from the product strength. The close proximity of the two numbers could result in confusion and/or error.

4. Assure child resistant closures are used for bottles intended to be a "unit of use" (e.g. 30 capsule size) in accordance with the Poison Prevention Act.

B. Insert Labeling

1. Dosage and Administration

a. The laboratory values presented to help evaluate dosage adjustments are cited with the greek presentation of micro (μ). Revise to the more acceptable "mcL" presentation, since "μl" may be confused with "mL" (milliliter). The USP Quality Review[1] includes "μg" on their list of potentially dangerous abbreviations for the same reasoning.

b. Consider repeating the information from the "laboratory tests" section of "Precautions" after the recommended dose sentence. Often health care professionals only read the dosage and administration section of the insert; thus including this information will help to assure the testing is performed. Thus the section will read:

> The recommended starting dose of Revlimid is 10 mg daily. A complete blood cell count.....weekly for the first 8 weeks of Revlimid treatment and monthly thereafter to monitor for cytopenias.

b. Consider the addition of the second paragraph from "geriatric use" section of "Precautions", which refers to the potential dosage adjustments for patients with impaired renal function.

c. Please review the formatting of this section. The copy received by our division is missing indentations and bulleting and therefore is difficult to follow. Please assure the formatting is consistent to prohibit confusion and improve ease of reading.

C. Patient Package Insert

Reference is made to the heading of "What are the possible side effects of Revlimid?" DMETS questions the organization and language of this section. The sponsor is using system organ classes as the organization key, which would likely be confusing for the average patient. Thus, the sponsor should give consideration to adjusting the presentation of the side effects for ease of comprehension. Please consider consulting the Division of Surveillance, Research and Communication Support for guidance and suggestions.

In summary, DMETS has no objection to the use of the proprietary name of Revlimid from a safety perspective. This is considered a final decision. However, if the approval of the NDA is delayed beyond 90 days from the signature date of this document, the name with its associated labels and labeling must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and/or established names from the signature date of this document. In addition, DMETS recommends implementation of the label and labeling revisions outlined in this memo to minimize potential errors with the use of this product. DMETS also recommends that the division consider submitting the patient package insert to the Division of Surveillance, Research and Communication Support for review and comment. DDMAC finds the name of Revlimid acceptable from a promotional perspective.

We would be willing to meet with the Division for further discussion if needed. If you have any questions or need clarification, please contact Diane Smith at 301-827-1998.

[1] USP Quality Review, Number 80, Issued on July 2004. Potentially Dangerous Abbreviations. WWW.USP.ORG/PATIENTSAFETY/NEWSLETTERS/QUALITYREVIEW/QR802004-07-01B.html.

NDA 21-880
HFD-109: Division Files/Carl Huntley, Project Manager
HFD-109: Richard Pazdur, Medical Officer
HFD-040: Catherine Gray, Regulatory Review Officer, DDMAC
HFD-040: Debi Tran, Regulatory Review Officer, DDMAC
HFD-420: Diane Smith, Project Manager, DMETS
HFD-420: Kim Culley, Safety Evaluator, DMETS
HFD-420: Alina Mahmud, Team Leader, DMETS

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

/s/

Alina Mahmud
6/27/05 11:48:13 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
6/27/05 11:55:09 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
6/28/05 03:57:09 PM
DRUG SAFETY OFFICE REVIEWER

MEMO OF FILING MEETING

NDA 21-880, Revlimid (lenalidomide, CC-5013) capsules
DATE: May 26, 2005

BACKGROUND: This NDA was received on April 11, 2005. The proposed indication for Revlimid is supported from study CC-5013-MDS-003. Revlimid is to be used in the treatment of patients with transfusion-dependent anemia due to low-or intermediate-1-risk myelodyplastic syndromes (MDS) associated with a deletion 5q cytogenic abnormality with or without additional cytogenetic abnormalities. A pre-NDA meeting was held on August 24, 2004. A CMC pre-NDA meeting was held on November 5, 2004. Celgene has received orphan drug status on January 29, 2004 and received fast track designation on April 11, 2004.

ATTENDEES: Robert Justice, Ann Farrell, Maitreyee Hazarika, Nallaperum Chidambaram, John Leighton, Anwar Goheer, Raji Sridhara, Brian Booth, Gene Williams, Edvardas Kaminskas

ASSIGNED REVIEWERS (including those not present at filing meeting):

Discipline	**Reviewer**
Medical:	Ann Farrell
Secondary Medical:	Maitreyee Hazarika
Statistical:	Yong-Chen Wang
Pharmacology:	Anwar Goheer
Statistical Pharmacology:	
Chemistry:	Hari Sarker
Environmental Assessment (already submitted)	Hari Sarker
Biopharmaceutical:	Gene Williams
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	Leslie Ball/Gan
Regulatory Project Management:	Carl Huntley
Other Consults:	DDMAC (Grillo), DMETS (Dallas),
ODS (Lu)	

Per reviewers, are all parts in English or English translation? YES	X	NO	☐

If not, explain:

CLINICAL FILE	X	REFUSE TO FILE	☐

• Clinical site inspection needed? YES	X	NO	☐

• Advisory Committee Meeting needed? YES	9/13/05 or 9/14/05	NO	☐

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A	☐	YES	☐	NO	☐

CLINICAL MICROBIOLOGY N/A	X	FILE	☐	REFUSE TO FILE	☐

STATISTICS N/A	☐	FILE	X	REFUSE TO FILE	☐

BIOPHARMACEUTICS FILE	X	REFUSE TO FILE	☐

- Biopharm. inspection needed? ☐ X
  YES NO

PHARMACOLOGY N/A	☐	FILE	X	REFUSE TO FILE	☐

• GLP inspection needed? YES	☐	NO	X

CHEMISTRY FILE	X	REFUSE TO FILE	☐

• Establishment(s) ready for inspection? YES	X	NO	☐

- Microbiology ☐ X
  YES NO

ELECTRONIC SUBMISSION:
Any comments: Issue of missing data sets – now fixed.

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐	The application is unsuitable for filing. Explain why:
X	The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
☐	No filing issues have been identified.
☐	Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1.☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

2.☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center
Director) or denying (for signature by ODE Director) an exception for review.

3.X Convey document filing issues/no filing issues to applicant by Day 74.

Carl Huntley
Regulatory Project Manager, HFD-150

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

/s/

Carl Huntley
7/12/05 12:47:56 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Celgene Corporation	April 7, 2005
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(908) 673-9000	(908) 637-2763
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE**
86 Morris Avenue Summit, New Jersey 07901	Not Applicable

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* NDA 21-880

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
lenalidomide	REVLIMID®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
3-(4'-amino-1,3-dihydro-1-oxo-2*H*-isoindol-2-yl)-2,6-piperidinedione	CC-5013, CDC-501, Imid 1, Imid 2, CI-B, Compound 8a, Revimid

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Capsule	5 and 10 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

REVLIMID® is indicated for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☒ ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: December 14, 2004

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Submission of final portion of a marketing application as provided under Section 506c of the Federal Food, Drug and Cosmetic Act

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED Not Applicable THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☒ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Please see attachment

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)
IND numbers: 60,100, —
DMF Numbers: —

This application contains the following items: *(Check all that apply)*	
☒	1. Index
☒	2. Labeling *(check one)* ☒ Draft Labeling ☐ Final Printed Labeling
☒	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☒	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☒	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☒	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☒	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☒	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☒	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☒	16. Debarment certification (FD&C Act 306 (k)(1))
☒	17. Field copy certification (21 CFR 314.50 (l)(3))
☒	18. User Fee Cover Sheet (Form FDA 3397)
☒	19. Financial Information (21 CFR Part 54)
☒	20. OTHER

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

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

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Gretchen Toolan	Gretchen Toolan, Director Regulatory Affairs	April 7, 2005
ADDRESS *(Street, City, State, and ZIP Code)*		Telephone Number
86 Morris Avenue, Summit, NJ 07901		(908) 673-9551

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

4 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(5) Draft Labeling

Celgene Corporation
86 Morris Avenue
Summit, New Jersey 07901
Tel 908-673-9000
Fax 908-673-9001

April 7, 2005

Richard Pazdur, MD
Director, Division of Oncology Drug Products
Center for Drug Evaluation and Research, HFD-150
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

NDA 21-880
REVLIMID® (lenalidomide)

Re: Submission of New Drug Application

Dear Dr. Pazdur:

Celgene Corporation (Celgene) is submitting the final portion of the New Drug Application NDA 21-880 for REVLIMID® (lenalidomide) under 21 CFR 314.500 Subpart H-Accelerated Approval of New Drugs for Serious or Life Threatening Illnesses, for use in the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. This letter serves as notification that the MDS submission is now complete. We draw your attention to the fact tha

The proposed indication for REVLIMID® (lenalidomide) is supported by clinical data from study CC-5013-MDS-003, "A Multicenter, Single-Arm, open-Label Study of the Efficacy and Safety of CC-5013 Monotherapy in Red Cell Transfusion Dependent Subjects with Myelodysplastic Syndromes Associated with a Del (5q) Cytogenetic Abnormality. This submission for approval based on a single study is consistent with guidance given to Celgene by the Oncology Division on August 24, 2004. At this pre-NDA meeting, FDA stated that in the context of a single-arm trial, the endpoint of transfusion independence would be interpretable if the results were outstanding, durable, and supported by objective evidence of a direct drug effect on transfusion requirements. Celgene believes that the results of the CC-5013-MDS-003 study achieve this standard by demonstrating that REVLIMID® (lenalidomide) produces sustained hematological and histological improvement as well as cytogenetic remission.

The MDS are life threatening and debilitating illnesses for which there are few treatment options. The severe anemia associated with low- to intermediate-1-risk MDS, including in patients with a deletion 5q cytogenetic abnormality, and the need for repeated RBC transfusions are major causes of morbidity. The only curative treatment for MDS is

allogeneic hematopoetic stem cell transplantation. Because of the advanced age of MDS patient, few are candidates for bone marrow transplantation. To date, no treatment modality has altered the natural course of MDS, and supportive care with antibiotics and transfusions is still considered the standard of care. Recently, azacitidine (Vidaza™, Pharmion) was approved in the United States for the treatment of MDS. Although azacitidine offers a new therapeutic option for patients with MDS, the overall response rate (complete and partial response) is <20% and the drug is administered subcutaneously. Celgene believes the results of the CC-5013-MDS-003 study show that REVLIMID® (lenalidomide) is an effective, well-tolerated, oral agent for the treatment of MDS that represents a clear benefit over available treatments.

Based on the above information, we are requesting priority review for this marketing application.

Celgene intends to confirm the clinical benefit of REVLIMID® (lenalidomide) in patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional chromosomal abnormalities in a Phase III multi-center double-blind, placebo-controlled, randomized study. The study is being conducted in Europe. The protocol, CC-5013-MDS-004, entitled " A Multicenter, Randomized, Double-Blind, Placebo-Controlled, 3-Arm Study of the Efficacy and Safety of 2 Doses of Lenalidomide Versus Placebo in Red Blood Cell (RBC) Transfusion-Dependent Subjects with Low- or Intermediate-1-Risk Myelodysplastic Syndromes (MDS) Associated with a Deletion (DEL) 5q[31] Cytogenetic Abnormality" was submitted to IND 60,100 in the Oncology Division on March 2, 2005 (Serial No. 529).

REVLIMID® (lenalidomide) was granted fast track designation (granted April 11, 2003) for the treatment of transfusion dependent MDS and orphan drug status for the treatment of MDS (granted January 29, 2004) Designation Request No. — This application, therefore, qualifies for the Orphan Exception under Section 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (the Act) and is not subject to a prescription drug user application fee. A completed Prescription Drug User Fee Cover Sheet (Form FDA 3397) was provided with the first portion of the application submitted on December 22, 2004. Furthermore, Celgene expects to be granted 7 years marketing exclusivity from the date of approval for the use of REVLIMID® (lenalidomide) in MDS, under Section 527(a)(3) of the Act.

Under Code of Federal Regulations (CFR) 314.55(d) the requirement to submit pediatric data does not apply to any drug for an indication or indications for which orphan drug designation has been granted. As REVLIMID® (lenalidomide) was granted orphan drug status for the treatment of MDS, Celgene is not submitting pediatric data nor requesting a pediatric waiver.

As advised by the Field office, a separate field copy of the NDA is not being submitted since this NDA is provided electronically.

Lenalidomide was adopted as the United States Adopted Name (USAN) for CC-5013 on December 31, 2003. Lenalidomide was approved by the WHO Nomenclature Committee and

attained the status of a proposed International Nonproprietary Name (INN) for CC-5013 on September 8, 2004.

REVLIMID® was submitted to the Division of Oncology Products on September 11, 2003 as a proposed trade name. On December 19, 2003 the Division notified Celgene that the Division of Medication Errors and Technical Support (DMETS) had no objection to the use of REVLIMID®

This NDA is a hybrid document. It is in Common Technical Document (CTD) format in the eNDA folder structure. Celgene's request to submit portions of the marketing application on a rolling basis was granted by FDA on December 14, 2004. The first portion of the rolling submission was submitted December 22, 2004 and consisted of the CMC and Nonclinical Sections and the following summaries; Quality Overall Summary, NonClinical Overview and NonClinical Written and Tabulated Summaries.

At the pre-NDA meeting, August 24, 2004, FDA requested that Celgene submit a proposal for the submission of safety summary information from studies other than the primary efficacy studies in MDS, that provided a robust dataset for assessing safety while allowing for a timely NDA submission data. The proposal also included plans for the 120-day update. The proposal was submitted on October 13, 2004 Serial No. 476.

The following portions of the marketing application are provided with this letter:

Module 1

	Comprehensive Table of Contents
1.1	Forms
1.2	Cover Letter
1.3	Administrative Information

Module 2	**Summaries**
2.1	CTD Table of Contents
2.2	CTD Introduction
2.5	Clinical Overview
2.7	Clinical Summary

Module 5	**Efficacy**
5.1	Table of Contents
5.2	Tabular Listings of All Clinical Studies
5.3	Clinical Study Reports
5.4	Literature References

The information on the enclosed CD-ROM is compliant with the following guidelines:

- "Guidance for Industry: Submitting Marketing Applications According to the ICH-CTD Format – General Considerations (August 2001)"
- "Guidance for Industry: Regulatory Submissions in Electronic Format; General Considerations (January 1999)"
- Guidance for Industry: Regulatory Submissions in Electronic Format; NDAs (January 1999)

Submission Size: 1.5 GB
Number of CDs: 3

The CD was certified to be virus-free using Symantec AntiVirus Corporate Edition Program 8.00.9374 with virus definition file version re.9, dated 3/31/2005 by Octagon Research Solutions Inc.

Please address any questions regarding NDA 21-880 to me at telephone number (908) 673-9551, facsimile number (908) 673-2763 or email gtoolan@celgene.com.

Yours truly,

Gretchen Toolan
Director, Regulatory Affairs

Enclosure

User Fee Cover Sheet (Form FDA 3397)

This form was submitted with the first portion of the New Drug Application 21-880 for REVLIMID® on December 22, 2004.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: December 31, 2006.

See Instructions on Reverse Side Before Completing This Form

. completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS
Celgene Corporation
86 Morris Avenue
Summit, N.J. 07901

2. TELEPHONE NUMBER *(Include Area Code)*
(908) 673-9551

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
21-880

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

3. PRODUCT NAME
Revlimid (lenalidomide)

6. USER FEE I.D. NUMBER
Not Applicable

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☒ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FORTHIS APPLICATION?
☐ YES ☒ NO
(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Gretchen Toolan	Gretchn Toolan, Director Regulatory Affairs	12/22/2004

FORM FDA 3397 (12/03)

N-503-1C
DUPLICATE

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
Tel 732-271-1001
Fax 732-271-4184

DEC 13 2004

December 10, 2004

Richard Pazdur, M.D.
Director, Division of Oncology Drug Products
Center for Drug Evaluation and Research/HFD-150
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

IND 60,100
Lenalidomide
(CC-5013) Capsules
Serial No.: 503

RE: MEETING MINUTES OF CMC PRE-NDA MEETING OF NOVEMBER 5, 2004

Dear Dr. Pazdur,

Enclosed please find Celgene's record of the meeting between FDA and Celgene Corporation held on November 5, 2004, to discuss the Chemistry, Manufacturing and Controls section of the New Drug Application to be submitted for lenalidomide (CC-5013) capsules.

Please do not hesitate to contact me with any questions or concerns at (732) 652-4566 or via email at megan.parsi@celgene.com

Sincerely,

Megan Parsi

Megan Parsi
Director, Regulatory Affairs

Enclosures

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

INVESTIGATIONAL NEW DRUG APPLICATION (IND)

(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

Form Approved: OMB No. 0910-0014.
Expiration Date: January 31, 2006
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSER
Celgene Corporation

2. DATE OF SUBMISSION
12/10/04

3. ADDRESS *(Number, Street, City, State and Zip Code)*
7 Powder Horn Drive
Warren, NJ 07059

4. TELEPHONE NUMBER *(Include Area Code)*
(732) 271-1001

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
Revlimid™, lenalidomide, amino isoindoline [3-(4'-aminoisoindoline-1'-one)-1-piperidine-2,6-dione], CC-5013

6. IND NUMBER *(If previously assigned)*
60,100

7. INDICATION(S) *(Covered by this submission)*
Myelodysplastic Syndromes, Multiple Myeloma and Solid Tumor

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED:
☐ PHASE 1 ☒ PHASE 2 ☐ PHASE 3 ☐ OTHER _____ *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR Part 314.420)*, AND PRODUCT LICENSE APPLICATIONS *(21 CFR Part 601)* REFERRED TO IN THIS APPLICATION.

/

10. ***IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.***

SERIAL NUMBER
0 5 0 3

11. THIS SUBMISSION CONTAINS THE FOLLOWING: ***(Check all that apply)***

☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)
☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):
☐ NEW PROTOCOL
☐ CHANGE IN PROTOCOL
☐ NEW INVESTIGATOR

INFORMATION AMENDMENT(S):
☐ CHEMISTRY/MICROBIOLOGY
☐ PHARMACOLOGY/TOXICOLOGY
☐ CLINICAL

IND SAFETY REPORT(S):
☐ INITIAL WRITTEN REPORT
☐ FOLLOW-UP TO A WRITTEN REPORT

☐ RESPONSE TO FDA REQUEST FOR INFORMATION
☐ ANNUAL REPORT
☒ GENERAL CORRESPONDENCE
☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED
☒ OTHER Meeting Minutes *(Specify)*

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST NOTIFICATION 21 CFR 312.7(d)

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	DIVISION ASSIGNMENT:
		IND NUMBER ASSIGNED:

12. **CONTENTS OF APPLICATION**

This application contains the following items: *(Check all that apply)*

- ☒ 1. Form FDA 1571 *[21 CFR 312.23(a)(1)]*
- 2. Table of Contents *[21 CFR 312.23(a)(2)]*
- 3. Introductory statement *[21 CFR 312.23(a)(3)]*
- ☐ 4. General Investigational plan *[21 CFR 312.23(a)(3)]*
- ☐ 5. Investigator's brochure *[21 CFR 312.23(a)(5)]*
- ☐ 6. Protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ a. Study protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ b. Investigator data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ c. Facilities data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ d. Institutional Review Board data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- ☐ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23(a)(7)]*
  - ☐ Environmental assessment or claim for exclusion *[21 CFR 312.23(a)(7)(iv)(e)]*
- ☐ 8. Pharmacology and toxicology data *[21 CFR 312.23(a)(8)]*
- ☐ 9. Previous human experience *[21 CFR 312.23(a)(9)]*
- ☐ 10. Additional information *[21 CFR 312.23(a)(10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☒ YES ☐ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☒ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

Robert Knight, M.D.
Executive Director, Clinical Oncology Research
Celgene Corporation

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

Rose Rogan, MD
Vice President, Worldwide Drug Safety
Celgene Corporation

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	
Megan Parsi Director, Regulatory Affairs	Megan Parsi	
18. ADDRESS *(Number, Street, City, State and Zip Code)*	19. TELEPHONE NUMBER *(Include Area Code)*	20. DATE
7 Powder Horn Drive Warren, NJ 07059	(732) 652-4566	12/10/04

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

and Drug Administration
(HFM-99)
. Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please **DO NOT RETURN** this application to this address.

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Megan Parsi	**From:** Maureen Pelosi
Fax: 732-271-4184	Fax: 301-827-4590
Phone: 732-652-4566	Phone: 301-594-5778 / Email:PELOSIM@CDER.FDA.GOV
Pages, including cover sheet: 8	Date: 29 NOV 04
Re: IND 60, 100 Serial #464 & #469 / preNDA CMC Meeting / MDS	

☐ Urgent ☐ For Review ☐ Please Comment ☐ Please Reply ☐ Please Recycle

● Dear Megan:

Attached are the pre NDA CMC minutes for CC-5013 in MDS.

Please phone me if I may be of further assistance,

Regards,

Maureen A. Pelosi, RPh
Senior Regulatory Project Manager

MEETING MINUTES

MEETING DATE: November 5, 2004 **TIME:** 2:30 PM **LOCATION:** WOC-2/ "G"

IND 60,100

Meeting Request Submission Date: 9/29/04 #464 MR
Response Date: 10/4/04
Briefing Document Submission Date: 10/7/04 #469 MP

DRUG: CC-5013/ lenalidomide(USAN)/ Revlimid™ capsules

SPONSOR/APPLICANT: Celgene Corporation

TYPE of MEETING:

1. **"B" – preNDA CMC**
2. **Proposed Indication:**

Revlimid is indicated for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with (*or* that have) a deletion 5q cytogenetic abnormality.

PARTICIPANTS:

FDA:

Nallaperum Chidambaram, Ph.D., CMC Team Leader (Meeting Chair)
Haripada Sarker, PhD, CMC Reviewer
Brian Booth,, PhD, OCPB Acting Team Leader
Sophia Abraham, Ph.D., OCBP Reviewer
Maureen Pelosi, RPh, Project Manager
Carl Huntley, RPh, Project Manager

INDUSTRY PARTICIPANTS: Celgene

Mr. Paul D'Angio, RPh.	Vice President, Technical Operations
Ms. Megan Parsi	Director, Regulatory Affairs
Mr. Larry Pflum	Senior Director, Project Management
Dr. Michael Vander Zwan	V. Pres., Corporate Quality Assurance & Compliance

PURPOSE OF MEETING:

The primary purpose of the meeting is to review and reach agreement with the Division on the CMC information required to support a marketing application under 21 CFR 312.80 Subpart E for the proposed indication.

MEETING OBJECTIVES:

The objective of the meeting is to provide an update regarding some of the issues discussed at the teleconference of November 18, 2003 and to gain concurrence with the Agency regarding the following:

- The proposed dissolution specification and conditions are acceptable
- Confirm that the amount of stability data available for the drug product is sufficient to justify a 24-month expiration-dating period
- Confirm that Celgene can file an additional drug product manufacturer with — of site-specific stability data considering that other supportive information as per SUPAC-IR will also be included in the application
- A biowaiver is acceptable for the 10 mg capsules which is the additional strength of the drug product
- Reach agreement on the executed batch records for which copies should be provided in the application
- Confirm the method of filing a new laboratory location for Celgene immediately post-approval

BACKGROUND:

A teleconference was held on November 18, 2003 to discuss the CMC development plans for CC-5013, during which Celgene stated that CC-5013 would be available in strengths of 5, 10 — capsules. The lead NDA filing will be for myelodysplastic syndrome (MDS) as a single indication for which the expected dose will be 5 -10mg/day, given orally. Therefore, the application will include 5 mg and 10 mg as the "to-be-marketed" doses for this indication, —. Celgene would like to re-visit with the FDA, some of the questions raised at the teleconference.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. **The proposed conditions provide discrimination not evidenced by the — — media. Does the agency agree that the proposed dissolution specifications and conditions acceptable?**

   FDA RESPONSE:

   This is a review issue. We recommend that you submit in the NDA Application a detailed rationale for the selection of your proposed dissolution method and specifications. Please include in the NDA Application, dissolution profiles in various conditions and media and comparative dissolution profiles for the proposed and current methods for both clinical and stability batches as per the Guidance for Industry on Dissolution Testing of Immediate Release Solid Oral Dosage Forms (http://www.fda.gov/cder/guidance/1713bp1.pdf).

2. **Will the amount of stability data available for the drug product be sufficient for filing in the initial application to justify a 24-month expiration-dating period for the drug product?**

   FDA RESPONSE:

   NO. 24-months expiration dating can't be considered with — — of stability data provided in the submission. Based on the quality of primary as well as supportive stability data, a reasonable extrapolation could be considered when an expiration dating period is determined.

   During the meeting, Celgene discussed their proposal for a Rolling Submission. They stated that the pre-clinical and CMC units would be sent first. They anticipate filing one CMC amendment to update primary and supportive stability data from three batches of each strength, during review.

3. **Does the Agency agree that Celgene can file an additional drug product manufacturer —) with — of site-specific stability data considering that other supportive information as per SUPAC-IR will also be included in the application**

   FDA RESPONSE:

   YES, your proposal appears to be acceptable. We also refer to the recommendation that was conveyed at the CMC telecon held on November 18, 2003.

4. **We intend to include two dosage strengths of 5 mg and 10 mg lenalidomide capsules in our marketing application that is scheduled for submission in the fourth quarter this year. As indicated in our teleconference of November 18, 2003, given that the 10 mg capsules have not yet been used in clinical studies, we will be requesting a waiver of the in-vivo bioequivalence study according to the FDA Guidance for Industry - Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations**

   We will have data supporting:

   a) the biopharmaceutical classification of high solubility and low permeability

   b) the clinical efficacy and safety of a 10 mg dose

   c) the linear pharmacokinetics between 5 and 400 mg using AUC

   d) the proportional similarity in composition between the 5 mg and 10 mg capsule

   e) the similarity in the dissolution of the 5 mg and 10 mg capsules in six media (based on f2 calculations

   With the above information we feel that we can satisfy the requirement of a biowaiver for the higher 10 mg strength of an immediate release capsule per the Bioavailability/Bioequivalence Guidance.

Does the agency agree that, for the biopharmaceutical classification of the drug and the type of formulation, a biowaiver request with the data listed above would be adequate to support a biowaiver for the 10 mg dose?

FDA RESPONSE:

A biowaiver cannot be granted without a review of the supporting data. We agree that the information described as points a-e could support a biowaiver request.

We recommend that you submit the above (a-e) supportive data to the IND with a request for a biowaiver response.

5. **With respect to the requirements for submission of executed batch records per 21 CFR 314.50 (d)(1)(ii)(b), we propose to include in the application, one representative executed batch record of a primary stability drug product batch, for each manufacturing facility, per strength. Accordingly, there will be a total of 4 batch records. Does the Agency agree with this approach?**

   FDA RESPONSE:

   Yes, your proposal is acceptable with the understanding that the executed batch record for other batches will be available in-house and may be requested at the time of inspection.

6. **Celgene may move its laboratory facilities to a new location — after the NDA is approved. Given that the same methods, equipment, personnel and SOPs will be used, we intend to submit this change post approval as a CBE supplement. Does the Agency concur with this approach?**

   FDA RESPONSE:

   Yes, you may submit a CBE supplement if the proposed site has previously been inspected for this purpose and that it has a satisfactory cGMP status.

ACTION ITEMS:

1. Celgene will submit a Rolling Submission proposal later in November.

There were no unresolved issues.

The meeting concluded at 3:25 PM.

Minutes Prepared by:

Maureen A. Pelosi, R.Ph.
Regulatory Project Manager

Concurrence Chair:

Nallaperum Chidambaram, Ph.D.
CMC Team Leader

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

/s/

Nallaperumal Chidambaram
11/29/04 05:10:38 PM