CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204026Orig1s000

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Application: 204026

Application Type: New NDA

Name of Drug: Pomalidomide Capsules

Applicant: Celgene Corporation

Submission Date: April 10, 2012

Receipt Date: April 10, 2012

1.0 Regulatory History and Applicant's Main Proposals

NDA 204026 Pomalidomide provides for the indication "(pomalidomide) in combination with dexamethasone is indicated for patients with relapsed and refractory multiple myeloma who have received at least two prior regimens of established benefit, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy."

This application is based on 4 clinical studies in 552 subjects in which pomalidomide (Pom) was evaluated as a single agent as well as in combination with low dose dexamethasone (Pom + Dex). Two studies (Study CC-4047-MM-002 [Phase 2] and Study IFM-2009-02) are considered primary for the evaluation of efficacy. These studies were designed similarly as multicenter, randomized evaluations of Porn in subjects with relapsed and refractory MM who had received prior treatment that included lenalidomide and bortezomib. Both studies included a treatment arm that evaluated Pom 4 mg 21/28day in combination with 40 mg dexamethasone. In addition, two supportive trials CC-4047-MM-001 (a phase 1 study) and PO-MM-PI-0010 (an investigator study) provide further safety and/or efficacy data in the relapsed and refractory multiple myeloma patient population.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format. The resubmitted PI will be used for further labeling review.

5.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

YES 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

NO 4. White space must be present before each major heading in HL.

Comment:

YES 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment:

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

YES 12. All text must be **bolded**.

Comment:

NO 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

YES 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment:

YES 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

YES 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

NO 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment: *Unapproved NDA. This section is not applicable.*

YES 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

YES 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment: *Unapproved NDA. This section is not applicable.*

Indications and Usage

N/A 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]."

Comment:

Dosage Forms and Strengths

YES 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment:

YES 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

YES 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

YES

30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

YES 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use

Selected Requirements of Prescribing Information (SRPI)

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

YES 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

NO 42. All text is **bolded**.

Comment:

NO 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

NO 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

NO 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

NO 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Comment:

NO 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Patient Counseling Information

NO 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment:

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

/s/

AMY C BAIRD
01/23/2013

JANET K JAMISON
01/24/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 204026 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: (b) (4) Established/Proper Name: Pomalidomide Dosage Form: Capsules Strengths: 1, 2, 3, and 4 mg		
Applicant: Celgene Corporation Agent for Applicant (if applicable): N/A		
Date of Application: 4/10/2012 Date of Receipt: 4/10/2012 Date clock started after UN: N/A		
PDUFA Goal Date: 2/10/2013	Action Goal Date (if different):	
Filing Date: 6/9/2012	Date of Filing Meeting: 5/30/2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): Pomalidomide in combination with dexamethasone is indicated for patients with relapsed and refractory multiple myeloma who have received at least two prior regimens of established benefit, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***		☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***		☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐		Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***		☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products

	☐ Other (drug/device/biological product)

☒ Fast Track ☐ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 066188	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***		X		
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***		X		
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?				
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**				
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs***				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:				

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***				

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*				
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?				
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	**X**			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?		X		
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature?	X			

Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] 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." Applicant may not use wording such as, "To the best of my knowledge…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	X			

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:		**X**		

Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***				
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***				
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]				
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***		X		Submitted in correspondence dated 4/12/2012
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	X			
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	X			
Is the PI submitted in PLR format?[4]	X			

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***		X		
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 3/19/2010 ***If yes, distribute minutes before filing meeting***	X			

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 9/13/2011 ***If yes, distribute minutes before filing meeting***	X			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 5/30/2012

BLA/NDA/Supp #: NDA 204026

PROPRIETARY NAME: [redacted] (b) (4)

ESTABLISHED/PROPER NAME: Pomalidomide

DOSAGE FORM/STRENGTH: Capsules/1, 2, 3, and 4 mg

APPLICANT: Celgene Corporation

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Pomalidomide in combination with dexamethasone is indicated for patients with relapsed and refractory multiple myeloma who have received at least two prior regimens of established benefit, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Amy Baird	Y
	CPMS/TL:	Janet Jamison/Ebla Ali Ibrahim	Y
Cross-Discipline Team Leader (CDTL)			
Clinical	Reviewer:	Saleh Ayache/R. Angelo DeClaro	Y
	TL:	Albert Deisseroth	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		

	TL:		

Clinical Pharmacology	Reviewer:	Rachelle Lubin	Y
	TL:	Julie Bullock/Bahru Habtemariam	Y
Biostatistics	Reviewer:	Yun Wang	Y
	TL:	Mark Rothmann	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Brenda Gehrke	Y
	TL:	Haleh Saber	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	William Adams	Y
	TL:	Janice Brown	Y
Quality Microbiology *(for sterile products)*	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Sarah Vee	N
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable***	☒ YES Date if known: Nov 2012 ☐ NO ☐ To be determined Reason:

○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• 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? **Comments**:	☐ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☐ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☐	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)

	• notify OMPQ (so facility inspections can be scheduled earlier)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

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

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(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.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

AMY C BAIRD
01/23/2013

JANET K JAMISON
01/24/2013

PMR/PMC Development Template (subpart H)

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	204-026
Product Name:	Pomalidomide
PMR Description:	Determine the effect of CYP3A Induction, which may DECREASE drug exposure, on the PK of Pomalidomide.

PMR Schedule Milestones:		
	Final Protocol Submission:	5/31/2013
	Trial Completion:	5/31/2014
	Final Report Submission:	9/30/2014
	Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☒ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☒ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

Pomalidomide is a substrate of CYP3A. Information on the effect of CYP3A induction on pomalidomide exposure was not submitted in the NDA. Concomitant use of CYP3A inducers may decrease the exposure of Pomalidomide AND THUS REDUCE EFFICACY.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

In vitro studies suggest that pomalidomide is a substrate of CYP3A. The relative contribution of CYP3A to pomalidomide metabolism is approximately 30%. Based on these findings, patients on strong or moderate CYP3A inducers may have decreased pomalidomide exposure. Therefore studies are needed to determine the clinical impact of CYP3A inducers. Appropriate labeling recommendations (e.g. dose adjustments) maybe needed for patients taking drugs that are inducers of CYP3A.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☒ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☒ Assess a known serious risk related to the use of the drug?
☒ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct a clinical trial to assess the influence of CYP3A inducers on pomalidomide exposure. The number of patients enrolled in the study should be sufficient to detect PK differences that would warrant dose adjustment recommendations in the label. The PK sampling scheme should be optimal to accurately estimate relevant PK parameters for the parent drug. A data analysis plan must be included in the protocol.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial

☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☒ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

___RCK_____
(signature line for BLAs)

PMR/PMC Development Template (FDAAA)

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	204-026
Product Name:	Pomalidomide
PMR Description:	Determine the effect of CYP3A Inhibition, which may increase drug exposure and thereby drug toxicity, on pomalidomide PK

PMR Schedule Milestones:		
	Final Protocol Submission:	5/31/2013
	Trial Completion:	5/31/2014
	Final Report Submission:	9/30/2014
	Other: _____	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☒ Unmet need
   - ☒ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☐ Other

   Pomalidomide is a substrate of CYP3A. Information on the effect of CYP3A inhibition on pomalidomide exposure was not submitted in the NDA. Concomitant use of CYP3A inhibitors may increase the exposure of Pomalidomide and thereby increase drug toxicity.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

   In vitro studies suggest that pomalidomide is a substrate of CYP3A. The relative contribution of CYP3A to pomalidomide metabolism is approximately 30%. Based on these findings, patients on CYP3A inhibitors may have increased pomalidomide exposure. Therefore studies are needed to determine the clinical impact of CYP3A inhibitors. Appropriate labeling recommendations (e.g. dose adjustments) may be needed for patients taking drugs that are inhibitors of CYP3A.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☒ Assess a known serious risk related to the use of the drug?
☒ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct a clinical trial to assess the influence of CYP3A inhibitors on pomalidomide exposure. The number of patients enrolled in the study should be sufficient to detect PK differences that would warrant dose adjustment recommendations in the label. The PK sampling scheme should be optimal to accurately estimate relevant PK parameters for the parent drug. A data analysis plan must be included in the protocol.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☒ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_RCK_____
(signature line for BLAs)

PMR/PMC Development Template (FDAAA)

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	204-026
Product Name:	Pomalidomide
PMR Description:	Food Effect Study – Determine the effect of food on absorption and PK of the drug in an appropriate population to enable description of food effect dosing information to be added to the label

PMR Schedule Milestones:	Final Protocol Submission:	2/28/2013
	Trial Completion:	12/31/2013
	Final Report Submission:	2/28/2014
	Other: _____	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☒ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☒ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

The effect of food on pomalidomide exposure has not been addressed. Food-effect studies should be conducted to guide the decisions to administer the drug with or without food.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Food effect was assessed as a secondary objective in a clinical study with 2 mg of pomalidomide. However, that study was not sufficient because the sponsor used a failed test formulation to assess food effect. Food effect was not evaluated with the final market formulation. The proposed PMR will determine whether the effect of food alters the pharmacokinetics of pomalidomide. This data is pertinent for labeling purposes.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☒ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct a food effect study. The number of patients enrolled in the study should be sufficient to detect PK differences that would warrant food effect recommendations in the label. The PK sampling scheme should be optimal to accurately estimate relevant PK parameters for the parent drug. A data analysis plan must be included in the protocol.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety

☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_RCK_____
(signature line for BLAs)

PMR/PMC Development Template (FDAAA)

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	204-026
Product Name:	Pomalidomide
PMR Description:	Determine the effect of hepatic impairment in patients with baseline hepatic impairment receiving pomalidomide, since the drug is metabolized by the liver per FDA guidance.

PMR Schedule Milestones:		
	Final Protocol Submission:	5/31/2013
	Trial Completion:	5/31/2015
	Final Report Submission:	9/30/2015
	Other: _____	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☒ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☒ Small subpopulation affected
   - ☐ Theoretical concern
   - ☐ Other

   Pomalidomide is metabolized in the liver. The influence of hepatic impairment on the safety, efficacy and pharmacokinetics of pomalidomide has not been provided in the NDA.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

   A human ADME study showed that pomalidomide is metabolized hepatically. Based on these findings, patients with baseline hepatic impairment maybe at an increased risk of liver toxicity, therefore the safety and PK properties of pomalidomide needs to be evaluated in a post marketing setting.

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3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**
  - ☐ Accelerated Approval (subpart H/E)
  - ☐ Animal Efficacy Rule
  - ☐ Pediatric Research Equity Act
  - ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☒ Assess a known serious risk related to the use of the drug?
  - ☒ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
  - ☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct a clinical trial in patients with hepatic impairment. The number of patients enrolled in the study should be sufficient to detect PK differences that would warrant dose adjustment recommendations in the label. The duration of the study should be sufficient to reasonably characterize potential safety issues. The PK sampling scheme should be optimal to accurately estimate relevant PK parameters for the parent drug. A data analysis plan must be included in the protocol.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial

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☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

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PMR/PMC Development Template (FDAAA)

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	204-026
Product Name:	Pomalidomide
PMR Description:	Conduct a QT Prolongation trial per the FDA guidance to assess the effect of Pomalidomide on the QT interval.

PMR Schedule Milestones:		
	Final Protocol Submission:	2/28/2013
	Trial Completion:	5/31/2014
	Final Report Submission:	9/30/2014
	Other: _____	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☒ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☒ Small subpopulation affected
- ☒ Theoretical concern
- ☐ Other

A QT study designed to assess whether there are any effects of pomalidomide on QT interval was not performed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Studies to assess QT prolongation potential of pomalidomide have not been performed. The intent of this study is to determine whether patients taking pomalidomide are at greater risk of QT/QTc interval prolongation.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct a clinical study to assess the QT prolongation potential with pomalidomide. We recommend submitting your study protocol for IRT review along with any cardiac safety data.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☒ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

RCK
(signature line for BLAs)

PMR/PMC Development Template (FDAAA)

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	204-026
Product Name:	Pomalidomide
PMR Description:	Renal impairment trial in patients with baseline renal impairment and those on chronic dialysis to determine the safety and PK in the renal impairment population, conducted per FDA guidance.

PMR Schedule Milestones:		
	Final Protocol Submission:	2/17/2012
	Trial Completion:	5/31/2015
	Final Report Submission:	9/30/2015
	Other: _____	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☒ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☒ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

Pomalidomide is excreted via the kidneys. The influence of renal impairment on the safety, efficacy and pharmacokinetics of pomalidomide has not been provided in the NDA

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Human ADME study results showed that pomalidomide and metabolites are excreted via the kidneys. Approximately 73% of radiolabeled pomalidomide dose was recovered in the urine. Based on these findings, patients with baseline renal impairment may have a decrease in pomalidomide clearance; therefore the safety and PK properties of pomalidomide needs to be evaluated in a post marketing setting.

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3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**
  - ☐ Accelerated Approval (subpart H/E)
  - ☐ Animal Efficacy Rule
  - ☐ Pediatric Research Equity Act
  - ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☒ Assess a known serious risk related to the use of the drug?
  - ☒ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
  - ☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct a renal impairment trial in patients with varying degrees of renal impairment including patients with mild, moderate, severe renal function and those on chronic dialysis. Conduct the study for sufficient duration in order to detect and assess safety and efficacy signals.

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Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

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PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	204-026
Product Name:	Pomalidomide
PMC Description:	Determine the effects of smoking (CYP1A2 Inducer) on PK of pomalidomide.

PMC Schedule Milestones:		
	Final Protocol Submission:	5/31/2013
	Study Completion:	5/31/2015
	Final Report Submission:	9/30/2015
	Other: _____	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☒ Unmet need
   - ☒ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☐ Other

   Pomalidomide is metabolized by CYP1A2. CYP1A2 is induceable by smoking. Information on the effect of CYP1A2 induction on pomalidomide exposure was not submitted in the NDA. Patients who smoke cigarettes may be at greater risk of reduced pomalidomide efficacy.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

   The relative contribution of CYP1A2 to pomalidomide metabolism is approximately 54%. Cigarette smoking may reduce pomalidomide AUC due to CYP1A2 induction; therefore reduced pomalidomide efficacy may be seen. The intent is to confirm whether cigarette smoking can impact pomalidomide exposure.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Because pomalidomide is a CYP1A2 substrate that is induced by smoking; the influence of smoking on the exposure to pomalidomide needs to be addressed. Evaluate the influence of smoking on the exposure to pomalidomide. Such an evaluation maybe conducted by pooling clinical data across different trials and looking at the influence of smoking on the exposure, safety, and effectiveness of pomalidomide.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 204026
Product Name: Pomalyst

PMR/PMC Description: PMR (Subpart H): Conduct a randomized controlled trial (MM-007) that isolates and demonstrates the efficacy and safety of pomalidomide in patients with previously treated multiple myeloma

PMR/PMC Schedule Milestones:

Final Protocol Submission:	MM/YYYY
Study/Trial Completion:	MM/YYYY
Final Report Submission:	MM/YYYY
Other: _____	MM/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☒ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

Patients with previously treated multiple myeloma have an incurable disease that confers a poor prognosis. The results of clinical trial MM-002, one of the trials submitted to support the NDA, showed a median overall survival of 14 months in a patient population that was heavily pretreated (median of 5 prior therapies).

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of the clinical trial would be to demonstrate the efficacy and safety of pomalidomide using a controlled trial designed to (1) show superiority (e.g., add-on design, active-control) and (2) isolates the treatment effect of pomalidomide. The Applicant has a current ongoing clinical trial that meets the design, MM-007. Clinical trial MM-007, titled "A Phase 3, Multicenter, Randomized, Open-Label Study to Compare the Efficacy and Safety of Pomalidomide, Bortezomib and Low-Dose Dexamethasone versus Bortezomib and Low-Dose Dexamethasone in Subjects with Relapsed or Refractory Multiple Myeloma" received SPA agreement on December 14, 2012.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☒ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required: MM-007 "A Phase 3, Multicenter, Randomized, Open-Label Study to Compare the Efficacy and Safety of Pomalidomide, Bortezomib and Low-Dose Dexamethasone versus Bortezomib and Low-Dose Dexamethasone in Subjects with Relapsed or Refractory Multiple Myeloma"

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☒ Other (provide explanation)
Randomized clinical trial

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☐ Has the applicant adequately justified the choice of schedule milestone dates?
☐ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 204026
Product Name: Pomalyst

PMR/PMC Description: PMR (FDAAA Safety): Conduct a randomized controlled trial (MM-003) of the combination of pomalidomide and dexamethasone in patients with previously treated multiple myeloma

PMR/PMC Schedule Milestones:

Final Protocol Submission:	MM/YYYY
Study/Trial Completion:	MM/YYYY
Final Report Submission:	MM/YYYY
Other: _____	MM/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☒ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

Patients with previously treated multiple myeloma have an incurable disease that confers a poor prognosis. The results of clinical trial MM-002, one of the trials submitted to support the NDA, showed a median overall survival of 14 months in a patient population that was heavily pretreated (median of 5 prior therapies).

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The Applicant should submit the results of a recently completed Phase 3 trial, MM-003, titled "A Phase 3, Multicenter, Randomized, Open-label Study to Compare the Efficacy and Safety of Pomalidomide in Combination with Low-Dose Dexamethasone versus High-Dose Dexamethasone in Subjects with Refractory or Relapsed and Refractory Multiple Myeloma".

Justification for FDAAA PMR: Previous clinical trials did not have an acceptable control arm to adequately describe the safety of pomalidomide.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☒ Assess a known serious risk related to the use of the drug?
☒ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required: MM-003 "A Phase 3, Multicenter, Randomized, Open-label Study to Compare the Efficacy and Safety of Pomalidomide in Combination with Low-Dose Dexamethasone versus High-Dose Dexamethasone in Subjects with Refractory or Relapsed and Refractory Multiple Myeloma"

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☒ Other (provide explanation)
Randomized clinical trial

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☐ Has the applicant adequately justified the choice of schedule milestone dates?
☐ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 204026
Product Name: Pomalyst

PMR/PMC Description: PMR (FDAAA Safety):
PMR (FDAAA Safety): Conduct an epidemiologic study to address the questions detailed below:
1. What is the failure rate for each of the different types of thromboembolic prophylaxis (e.g., antiplatelet or anticoagulant therapy) for multiple myeloma patients treated with a pomalidomide-containing regimen?
2. What is the failure rate for each type of Deep Vein Thrombosis (DVT) treatment (e.g., dose-adjusted heparin, low molecular weight heparin, coumadin, or other oral anticoagulants) for those patients with multiple myeloma and a DVT who continue to receive ongoing treatment with pomalidomide?
3. What is the failure rate for each type of post-DVT thromboembolic prophylaxis for those patients with multiple myeloma and a DVT who continue to receive ongoing treatment with pomalidomide?
This prospective epidemiologic study will enroll select patients identified in the (b) (4) program, and collect the necessary additional data on these patients to further evaluate occurrences of thrombosis and anticoagulant use.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	MM/YYYY
Study/Trial Completion:	MM/YYYY
Final Report Submission:	MM/YYYY
Other: _____	MM/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☒ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

Patients with previously treated multiple myeloma have an incurable disease that confers a poor prognosis. The results of clinical trial MM-002, one of the trials submitted to support the NDA, showed a median overall survival of 14 months in a patient population that was heavily pretreated (median of 5 prior therapies).

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Justification for FDAAA PMR: Immunomodulatory class of drugs are associated with an increased risk of venous thromboembolic events. The clinical trials to support pomalidomide approval do not adequately characterize the risk of venous thromboembolic events and most appropriate prophylaxis regimen.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**
  - ☐ Accelerated Approval (subpart H/E)
  - ☐ Animal Efficacy Rule
  - ☐ Pediatric Research Equity Act
  - ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☒ Assess a known serious risk related to the use of the drug?
  - ☒ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Epidemiologic study in selected patients identified in (b) (4) program.

Required

☒ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
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☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?

☒ Are the objectives clear from the description of the PMR/PMC?
☐ Has the applicant adequately justified the choice of schedule milestone dates?
☐ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	December 21, 2012
To:	Ann Farrell, MD Director **Division of Hematology Products (DHP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Latonia M. Ford, RN, BSN, MBA Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	TRADENAME (pomalidomide)
Dosage Form and Route:	capsules
Application Type/Number:	204026
Applicant:	Celgene Corporation

1 INTRODUCTION

On April 10, 2012, Celgene Corporation submitted Original New Drug Application (NDA) 204026 for TRADENAME (pomalidomide) capsules. The Applicant's proposed indication for TRADENAME (pomalidomide) capsules is for patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including bortezomib [redacted] (b) (4) and have demonstrated disease progression on the last therapy.

On December 13, 2012, the Division of Hematology Products (DHP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for TRADENAME (pomalidomide) capsules.

This review is written in response to a request by the Division of Hematology Products (DHP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Medication Guide for TRADENAME (pomalidomide) capsules.

The Risk Evaluation and Mitigation Strategy (REMS) is being reviewed by the Division of Risk Management (DRISK) and will be provided to DHP under separate cover.

2 MATERIAL REVIEWED

- Draft TRADENAME (pomalidomide) capsules MG received on April 10, 2012, and received by DMPP on December 13, 2012.
- Draft TRADENAME (pomalidomide) capsules Prescribing Information (PI) received on April 10, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on December 13, 2012.
- Approved REVLIMID (lenalidomide) comparator labeling dated May 9, 2012.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the MG is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

LATONIA M FORD
12/21/2012

BARBARA A FULLER
12/21/2012

LASHAWN M GRIFFITHS
12/21/2012

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: December 14, 2012

To: Amy Baird, Regulatory Project Manager
Division of Hematology Products (DHP)

From: Nisha Patel, Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)

Subject: Comments on draft labeling (Package Insert) for Trade Name™ (pomalidomide capsules) 1 mg, 2 mg, 3 mg, and 4 mg capsules
NDA 204026

In response to your consult dated May 30, 2012, we have reviewed the draft Package Insert (PI) for pomalidomide capsules and offer the following comments. DPDP has made these comments using the version dated, 11-6-2012 v3. We have also taken into consideration the labeling for Revlimid® (lenalidomide) capsules, for oral use.

Section	Statement from draft	Comment
Highlights, Dosage and Administration	4 mg/day taken orally on days 1-21 of repeated 28-day cycles until disease progression. (b) (4)	Please consider including the statement, "Treatment is continued or modified based upon clinical and laboratory findings" from the Dosage and Administration section of the full PI to ensure consistency between the Highlights section and full PI. We note that a similar statement appears in both Dosage and Administration sections of the Revlimid PI (Highlights and full PI). Please also consider including a cross-reference (2.1) in the Highlights section to the full PI.
Highlights, Warnings and Precautions		Please consider including risk information about the Warnings and Precautions associated with pomalidomide, such as "Hematologic Toxicity," "Thromboembolism," and "Allergic

Section	Statement from draft	Comment
		Reactions," in the Highlights section to ensure consistency with the full PI.
Highlights, Adverse Reactions	Most common adverse reactions (b) (4) (6.1)	We note that many adverse reactions that occur in ≥ 20% of pomalidomide treated patients (listed in Table 2) do not appear in the Highlights section. Please revise the Highlights section to ensure consistency with the full PI.
1.1 Indications and Usage, Multiple Myeloma	Trade Name (b) (4)	We note that the bolded terms were deleted from the Highlights, Indications and Usage section but are included in the full PI (emphasis added). Additionally, we note that the statement (b) (4) (emphasis added) appears in the Highlights, Indications and Usage section but not in the full PI. Please revise to ensure consistency between the Highlights section and full PI.
8.6 Use in Specific Populations, Geriatric Use	(b) (4)	Is this statement supported by substantial evidence? We recommend deleting this statement because it could be used promotionally to make efficacy claims based on subgroup analyses.
14.1 Clinical Studies, Multiple Myeloma		We note that this section includes unapproved dosing for pomalidomide. Please consider including a statement indicating that the Clinical Studies section contains information related to unapproved dosing.
17.1 Patient Counseling Information		Please consider including information describing "Hematologic Toxicity" and "Thromboembolism" to communicate important risk information to patients and ensure consistency with the Warnings and Precautions section of the full PI.

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/s/

NISHA PATEL
12/14/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label and Labeling Review

Date:	December 6, 2012
Reviewer:	Kevin Wright, PharmD Division of Medication Error and Prevention Analysis
Team Leader:	Yelena Maslov, PharmD Division of Medication Error and Prevention Analysis
Division Director	Carol A. Holquist, RPh Division of Medication Error and Prevention Analysis
Drug Name and Strength(s):	Pomalyst (Pomalidomide) Capsules 1 mg, 2 mg, 3 mg, and 4 mg
Application Type/Number:	NDA 204026
Applicant/sponsor:	Celgene Corporation
OSE RCM #:	2012-2633

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 Introduction 1
1.1 Regulatory History 1
1.2 Product Information 1
2 Methods and Materials Reviewed 1
3 Results and Recommendations 2
Appendices 4

1 INTRODUCTION

This review evaluates the proposed container labels and insert labeling for Pomalidomide under NDA 204026 for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

The Applicant submitted labels and labeling for Pomalidomide under NDA 204026 on April 10, 2012.

1.2 PRODUCT INFORMATION

The following product information is provided in the April 10, 2012 NDA submission.

- Active Ingredient: Pomalidomide
- Indication of Use: Treatment of relapsed and refractory multiple myeloma in combination with Dexamethasone in patients who have failed Lenalidomide and Bortezomib.
- Route of Administration: Oral
- Dosage Form: Capsules
- Strength: 1 mg, 2 mg, 3 mg, and 4 mg
- Dose and Frequency: Take 4 mg by mouth daily for 21 days of a 28 day cycle. The dose may be reduced by 1 mg if hematologic toxicities are experienced.
- How Supplied: 21 count and 100 count bottles
- Storage: Store at (b) (4) excursions permitted to 15° C to 30° C (59° to 86° F)
- Container and Closure System: Child resistant high density polyethylene (HDPE) bottles
- (b) (4) program: this is the proposed REMS program for this product where prescribers and pharmacists register with the program to prescribe and dispense the product to patients who are enrolled in the program. Pomalidomide is a thalidomide analogue. Thalidomide is a known human teratogen that causes severe life threatening birth effects.

2 METHODS AND MATERIALS REVIEWED

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Container Labels submitted April 10, 2012 (Appendices A through D)
- Insert Labeling submitted April 10, 2012 (no image)

3 RESULTS AND RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. Container Labels 1 mg, 2 mg, 3 mg, and 4 mg

1. Ensure the established name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Additionally, the established name should have a prominence commensurate with the prominence of the proprietary name in accordance with 21 CFR 201.10(g)(2).
2. Delete or minimize the graphic that appears to the left of the proprietary name as this graphic competes for the end user's attention with the proprietary name.
3. Ensure the proprietary name on the container label is presented in title case (i.e. Pomalyst) to ensure the readability of the proprietary name.

B. Insert Labeling

a. Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice's List of Error-Prone Abbreviations, Symbols, and Dose Designations appear in the Highlights of Prescribing and Dosage and Administration sections of package insert.[2] As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products. Thus, please revise the those abbreviations, symbols, and dose designations in the body of the text as follows:

- Revise the "/" symbol appearing throughout the Dosage and Administration section to read "per".
- Revise the '≤' and '≥'symbols appearing in the body of the text of sections 2.1 (Dose Modifications), to read "less than or equal to" and "more than or equal to" respectively.
- Information regarding product administration should be appear together. As such, revise the statement (b) (4) (b) (4)

[2] http://www.ismp.org/Tools/errorproneabbreviations.pdf, Last accessed 10/28/2009.

If you have further questions or need clarifications, please contact Sue Kang, OSE project manager, at 301-796-4216.

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/s/

KEVIN WRIGHT
12/06/2012

YELENA L MASLOV
12/06/2012

CAROL A HOLQUIST
12/07/2012

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: September 27, 2012

TO: Amy C. Baird, Regulatory Project Manager
Saleh Ayache, M.D., Medical Officer
Angelo De Claro, M.D., Medical Offier
Albert Deisseroth, M.D., Ph.D. Team Leader
Division of Hematology Products (DHP)

FROM: Anthony Orencia, M.D., F.A.C.P.
Medical Officer, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan D. Thompson, M.D.
Acting Branch Chief, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 204026

APPLICANT: Celgene Corporation

DRUG: pomalidomide

NME: Yes

THERAPEUTIC CLASSIFICATION/REVIEW: Standard Review

INDICATION: multiple myeloma

CONSULTATION REQUEST DATE: June 7, 2012 (signed)

INSPECTION SUMMARY GOAL DATE: December 12, 2012 (original)

DIVISION ACTION GOAL DATE: February 9, 2013

PDUFA DATE: February 9, 2013

I. BACKGROUND:

Standard first-line treatment for multiple myeloma patients with adequate performance status is a 3 to 4 month induction with thalidomide plus high-dose dexamethasone or a combination regimen consisting of vincristine, doxorubicin and high-dose dexamethasone. This treatment is followed by autologous stem cell transplantation that is effective in up to 10% of multiple myeloma patients using this therapeutic approach. Multiple myeloma patients who are not candidates for stem cell transplantation are given the chemotherapy regimen alone. Recently approved therapies included lenalidomide and bortezomib for those who had relapses or failed therapies. While survival depends on the extent of the multiple myeloma, patients factors such as co-morbidities or responses to treatments, or markers for aggressive multiple myeloma disease activity, these patients overall have a poor prognosis.

Pomalidomide (CC-4047) is an immuno-modulatory derivative of thalidomide reported to be more potent than thalidomide at inhibiting TNF-alpha in vitro. This drug, similar to other immuno-modulatory analogs such as lenalidomide, has the potential for reducing toxicity experienced with thalidomide, such as sedation, peripheral neuropathy, constipation and deep vein thrombosis.

A single adequate Phase 1/2 clinical trial was submitted in support of the applicant's NDA. Three domestic sites were selected for audit plus the Sponsor (Celgene Corporation).

Study CC-4047-MM-002

CC-4047-MM-002 was a Phase 1/2, multicenter, randomized, open-label, dose-escalation study that evaluated the safety and efficacy of oral CC-4047 alone and in combination with low dose oral dexamethasone in patients with relapsed and refractory multiple myeloma. Eligible patients received at least two prior therapies and all patients received prior treatment that included lenalidomide and bortezomib, and had measurable disease. This clinical site audit focused on the Phase 2 component of the study. The Phase 2 study randomized subjects to oral CC-4047 plus low-dose dexamethasone *versus* oral CC-4047 alone. The objective of this Phase 2 study was to determine the efficacy of CC-4047 alone and in combination with low-dose dexamethasone as treatment for patients with relapsed and refractory multiple myeloma.

All efficacy evaluations were conducted using the intent-to-treat (ITT) population, with progression free survival (PFS) identified in the protocol as the primary efficacy endpoint. Progression-free survival was defined as the time from randomization to the first documentation of disease progression or death from any cause during the study, whichever occurred earlier.

II. RESULTS:

Name of CI City, State	Protocol/Study Site	Insp. Date	Final Classification*
David S. Siegel, M.D. Hackensack, NJ	Protocol CC-4047-MM-002 Site #101	July 5 to 25, 2012	Preliminary: VAI
Paul Gerard Guy Richardson, M.D. Boston, MA	Protocol CC-4047-MM-002 Site #102	July 24 to August 1, 2012	Preliminary: NAI
Craig Hofmeister, M.D. Columbus, OH	Protocol CC-4047-MM-002 Site #108	July 12 to 18, 2012	NAI
Celgene Corporation Summit, NJ	Sponsor	August 7 to September 12, 2012	Preliminary: VAI

*Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability
OAI = Significant deviations from regulations. Data unreliable/Critical findings may affect data integrity.
Preliminary= The Establishment Inspection Report (EIR) has not been received and findings are based on preliminary communication with the field.

CLINICAL STUDY SITE INVESTIGATORS

1. David S. Siegel, M.D./Protocol CC-4047-MM-002 Site #101
Hackensack, NJ

a. What was inspected:
The inspection was conducted in accordance with Compliance Program 7348.811, from July 5 to 25, 2012. A total of 36 subjects were screened and enrolled, 34 subjects were randomized, and five subjects completed the study.

A 100% of the informed consent documents were inspected. An audit of 15 subjects' records was conducted. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. General observations/commentary:
Source documents for randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the primary study endpoint were verifiable at the study site. However, per DHP, a central adjudication committee reviewed the primary and secondary efficacy endpoints. There was no under-reporting of serious adverse events. There were no limitations during conduct of the clinical site inspection by ORA staff.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. However, a Form FDA 483 (List of Inspectional Observations) was issued at the end of the inspection for not maintaining adequate and accurate records.

Specifically, the clinical study site did not have adequate investigational drug disposition records for the quantity of drugs returned. For example, three subject's Investigational Agent Accountability Records and Investigational Product Return Packing Lists did not match the number of capsules returned, by two to five capsules.

The above observation does not have a critical impact on data reliability and integrity for this NDA.

c. Assessment of data integrity:
Data submitted by this clinical site appear acceptable for this specific indication.

Note: Observations noted above are based on preliminary communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

2. Paul Gerard Guy Richardson, M.D./ Protocol CC-4047-MM-002 Site #102
Boston, MA

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from July 24 to August 1, 2012. There were 2 study sites inspected for the Phase 2 segment of this study: (1) At the (b) (4) study site, 44 subjects were screened, 38 subjects were enrolled into the study, 37 subjects were randomized and treated, 25 subjects discontinued from the study, and 11 subjects were still on "follow-up status" at the time of the clinical audit, and (2) At the (b) (4) study site, 8 subjects were screened, 5 subjects were enrolled into the study, 5 subjects were randomized and treated, 4 subjects discontinued from the study, and one patient was still on "follow-up status" at the time of the clinical audit.

An audit of 23 enrolled subjects' records was conducted. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed Consent documents for 21 enrolled subjects and Sponsor-generated correspondence were also inspected.

b. General observations/commentary:
Source documents, for randomized subjects whose records were audited, were verified against the case report forms and NDA subject line listings and no discrepancies were found. Source documents for the primary study endpoint were verifiable at the study site. However, per DHP, a central adjudication committee reviewed the primary and secondary efficacy endpoints. There was no under-reporting of serious adverse events. There were no limitations during conduct of the clinical site inspections by ORA staff.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 (List of Inspectional Observations) was issued at the end of the inspection.

c. Assessment of data integrity:
Data submitted by this clinical site appear acceptable for this specific indication.

Note: Observations noted above are based on preliminary communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

3. Craig Hofmeister, M.D./Protocol CC-4047-MM-002 Site #101
Columbus, OH

a. What was inspected:
The inspection was conducted in accordance with Compliance Program 7348.811, from July 12 to 18, 2012. At this site, 24 subjects were screened, 19 subjects were enrolled, and 11 subjects completed the study (Note: 8 subjects were still on study at the time of the clinical site audit).

An audit of 19 subjects' records was conducted. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. General observations/commentary:
Source documents, for randomized subjects whose records were audited, were verified against the case report forms and NDA subject line listings. Source documents for the primary study endpoint were verifiable at the study site. However, per DHP, a central adjudication committee reviewed the primary and secondary efficacy endpoints. There were no limitations during conduct of the clinical site inspections by ORA staff.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 (List of Inspectional Observations) was issued at the end of the inspection.

The following observations of interest were discussed with DHP, and were determined not to be critical. These study protocol deviations were discussed by the FDA Office of Regulatory Affairs (ORA) field staff at the close-out discussion with the site's management and principal investigator, Dr. Hofmeister. No evidence of significant regulatory violations was provided in ORA's Establishment Inspection Report (EIR).

(1) Six patients, who signed initial informed consent form documents, did not sign the consent documents during their next visit following the approval of informed consent form Version 4 [IN3] along with Protocol Amendment #3, on December 9, 2010. These patients (Subjects #1083004, #1083008, #1083011, #1083012, #1083022 and #1083023) eventually signed the updated version of the informed consent form documents.
(2) An unspecified serious adverse event for Subject #1083002 occurred between December 12 and 18, 2010. The event was reported on January 28, 2010. Further, Subject #1083009 suffered a hip fracture; this event occurred between January 31 and February 15, 2012. The event was reported on March 30, 2012. These two late reports of serious adverse events were captured and reported in the NDA submission to the Agency.
(3) Subject #1083005 was diagnosed with "stable" multiple myeloma on February 18, and 25, 2012 based on radiographic findings. An MRI performed on March 8 and reported on March 9 indicates "progressive" multiple myeloma. However, the "InForm ITM" entry from March 12 indicates "stable" multiple myeloma. The "InForm ITM" audit trail from October 5, 2010 indicates that a change was made to that entry, but does not note what change was made or why. DHP stated that a final determination will be made as to the status of this patient in the division's efficacy analyses.

The above findings were discussed with the DHP Medical Team, who did not consider the above findings would have a significant impact on safety and efficacy assessments for this NDA.

c. Assessment of data integrity:
Data submitted by this clinical site appear acceptable for this specific indication.

SPONSOR

4. Celgene Corporation
Summit, NJ

a. What was inspected:
The inspection was conducted in accordance with Compliance Program 7348.810, from August 7 to September 12, 2012.

The inspection evaluated the following: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed Form FDA 1572s, monitoring reports, drug accountability, and training of staff and site monitors.

b. General observations/commentary:
The Sponsor did not maintain adequate oversight of the clinical trial. Monitoring of the investigator sites was not considered adequate, especially with respect to Investigational Product (IP) packaging, disposition, and drug accountability. A Form FDA 483 was issued at the end of the Sponsor inspection. Some relevant examples are listed below:

(1) The Sponsor inadequately monitored the study for study drug disposition and drug accountability.
For example:
(a) Per the study monitoring plan, drug accountability must be performed by the Clinical Research Associate monitor at every monitoring visit. However, the monitor did not check for investigational product accountability for 20 of 66 monitoring visits at Site #101, 13 of 60 monitoring visits at Site #102, and 19 of 38 monitoring visits at Site #108.
(b) The monitor did not document adequately drug accountability for four instances in the Monitoring Visit Report and Investigational Product Return Packing List for Site #101.
(c) The drug disposition records did not include the lot numbers and quantities of all investigational drug product destroyed by a party vendor.

(2) Per Study Drug Packaging and Labeling, Section 11.4 of the Study Protocol, labels of the investigational drug product did not include the following specific dosing instruction in the label: “Take 2 hours before or 2 hours after eating.”

OSI Medical Officer’s Note:
The above observations are considered minor regulatory deficiencies. These non-critical findings have no significant impact on data reliability.

c. Assessment of data integrity:
The study appears to have been conducted adequately. Data submitted by this Sponsor appear acceptable in support of the respective indication

Note: Observations noted above are based on preliminary communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

For this Phase 1/2 randomized, open-label study, three U.S. clinical investigator sites and the Sponsor were inspected in support of this application. The Phase 2 part of this study was mainly inspected.

No regulatory deficiencies were observed for Paul Gerard Guy Richardson, M.D. (Site #102) and Craig Hofmeister, M.D. (Site #108).

Minor regulatory deficiencies were observed for David S. Siegel, M.D. (Site #101) and the Sponsor, mainly related to study drug accountability. DHP noted that these observations were not critical.

Based on review of inspectional findings for these clinical investigators, the study data collected appear generally reliable in support of the requested indication.

Note: Observations noted above, for the above Clinical Sites #101 and #102 and Sponsor, are based on the preliminary communications from the field investigators; an inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIRs.

{See appended electronic signature page}

Anthony Orencia, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan D. Thompson, M.D.
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/s/

ANTHONY J ORENCIA
09/27/2012

SUSAN D THOMPSON
09/27/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	August 24, 2012
Reviewer:	Sarah K. Vee, PharmD, Safety Evaluator Division of Medication Prevention and Analysis
Team Leader	Yelena Maslov, PharmD, Acting Team Leader Division of Medication Prevention and Analysis
Division Director	Carol A. Holquist, RPh Division of Medication Prevention and Analysis
Drug Name(s) and Strength(s):	(b) (4) (Pomalidomide) Capsules, 1 mg, 2 mg, 3 mg, 4 mg
Application Type/Number:	NDA 204026
Applicant/Sponsor:	Celgene Corporation
OSE RCM #:	2012-922

*** This document contains proprietary and confidential information that should not be released to the public.***

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2.1 Labels and Labeling 2
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1 INTRODUCTION

This review evaluates the proposed container label and insert labeling for (b) (4) NDA 204026, for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

Pomalidomide was submitted under IND 066188 and received fast track status on December 15, 2011, based upon the unmet medical need for this patient population. NDA 204026 was submitted on April 10, 2012.

This drug has a proposed REMS program called (b) (4) where prescribers and pharmacists registered with the program can prescribe and dispense the product to patients who are registered and meet all the conditions of the program. The proposed REMS program includes the following components[1]:

- Medication Guide
- Elements to Assure Safe Use (ETASU)
    - Prescriber certification, patient registration so dispensing is under documented safe use condition and patient subject to monitoring (monthly surveys), and pregnancy registry
- Implementation System
    - Product tracking, Call Center, Computer Systems, Written Procedures, Pharmacy Audits
- Assessment Reports

1.2 PRODUCT INFORMATION

The following product information is provided in the April 12, 2012 New Drug Application submission.

- Active Ingredient: Pomalidomide
- Indication of Use: in combination with dexamethasone is indicated for patients with relapsed and refractory multiple myeloma who have received at least 2 prior regimens of established benefit, including both lenalidomide and bortezomib and have demonstrated disease progression on the last therapy.
- Route of Administration: oral
- Dosage Form: capsules
- Strengths: 1 mg, 2 mg, 3 mg, 4 mg
- How Supplied: Bottles containing 21 capsules and 100 capsules
- Storage: Store at (b) (4) excursions permitted to 15° to 30°C (59° to 86°F)

[1] Celgene Pomalidomide Capsules NDA 204026 FDA Orientation Meeting Presentation; June 8, 2012.

- Container and Closure Systems: Packaged in high density polyethylene (HDPE) bottles with child resistant closures.
- Dose and Frequency: 4 mg once daily on days 1 to 21 of repeated 28 day cycles until disease progression. Reduce dose by 1 mg for toxicities.

Toxicity	Dose Modification
Neutropenia • Absolute Neutrophil Count (ANC) less than 500/microliter or Febrile neutropenia (fever greater than or equal to 38.5 °C and ANC less than 1,000/microliter) • ANC return to greater than or equal to 500/microliter	Interrupt treatment, follow Complete Blood Count (CBC) weekly. (b) (4) Resume at 3 mg daily.
• For each subsequent drop less than 500/microliter • Return to greater than or equal to 500/microliter	Interrupt treatment Resume at 1 mg less than the previous dose
Thrombocytopenia • Platelets less than 25,000/microliter • Platelets return to greater than 50,000/microliter	Interrupt treatment, follow CBC weekly Resume treatment at 3 mg daily
• For each subsequent drop less than 25,000/microliter • Return to greater than or equal to 50,000/miroliter	Interrupt treatment Resume at 1 mg less than previous dose.

2 METHODS AND MATERIALS REVIEWED

We reviewed the (b) (4) container labels and package insert labeling submitted by the Applicant.

2.1 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,[2] the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted April 10, 2012 (Appendix A)
- Insert Labeling submitted April 10, 2012 (no image)

3 CONCLUSIONS

DMEPA concludes that the proposed container label can be improved to increase the prominence of important information on the label. Additionally, DMEPA concludes that the package insert could be improved by revising dangerous abbreviations, dose designations, and abbreviations for laboratory values and drug names.

[2] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

4 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. Container Label

- Delete or minimize the graphics around the proprietary name as it may distract from the prominence of the proprietary and the established names.
- Increase the prominence of the established name (which includes dosage form). Ensure the size of the established name is at least ½ the size of the letters comprising the proprietary name and has prominence consistent with the proprietary name (type, size, color, font) in accordance with 21 CFR 201.10 (g)(2).
- Relocate the statement "Dispense with Medication Guide" to the principle display panel to increase the prominence of this statement in accordance with 21 CFR 208.24. We also recommend revising the statement to read "PHARMACIST: Dispense attached Medication Guide to each patient".

B. Insert Labeling

1. Dosage and Administration in Highlights and Full Prescribing Information (Section 2.1, 2.2, and Table 1).
    - Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice's List of Error-Prone Abbreviations, Symbols, and Dose Designations appear throughout the package insert[3]. As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products. Thus, please revise the those abbreviations, symbols, and dose designations as follows:
        - Revise all instances of the symbols '<', '>', '≤', and '≥' to read "less than", "greater than", "less than or equal to", and "greater than or equal to." The symbols '<' and '>'are dangerous abbreviations that appear on the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations because these symbols are often mistaken and used as opposite of intended.
        - Revise the insert labeling to use the word "to" instead of a hyphen when referencing a range of values, such as Days 1 - 21. The hyphen may be misinterpreted as a negative or minus sign.
        - Revise all instances of 'μL' to read 'microliter' because this abbreviation has been interpreted as milliliter (mL).

[3] http://www.ismp.org/Tools/errorproneabbreviations.pdf, Last accessed 10/28/2009.

- Revise all instances of '/' and state the intended meaning (i.e. 'Grade 3/4' to 'Grade 3 or 4' and '21/28' to read '21 of 28 days'). The '/' symbol could be interpreted as 'or'.

2. Highlights of Prescribing Information:
   - Dosage and Administration
     - Revise the statement "4 mg/day" to read "4 mg once daily" to improve readability and to avoid confusion.
3. Full Prescribing Information
   - Dosage and Administration
     - Delete the statement '(21/28 days)' in the Multiple Myeloma section. This statement is not necessary and may cause confusion since the dosing interval is already spelled out as 'Days 1 – 21 of repeated 28-day cycles.'
   - Dose Adjustments for Toxicities: Table 1
     - Spell out 'ANC' to read 'Absolute Neutrophil Count' and put 'ANC' in parenthesis for the first time you refer to this count.
     - Place the 'degree (^{o})' symbol in the statement 'fever ≥ 38.5 C'.
     - Spell out 'CBC' to read 'Complete Blood Count' and put 'CBC' in parenthesis for the first time you refer to this count.
     - Revise (b) (4) (b) (4)
   - Dosage Forms and Strengths
     - Insert the 'mg' after each strength to read 1 mg, 2 mg, 3 mg, and 4 mg.

If you have further questions or need clarifications, please contact Sue Kang, OSE project manager, at 301-796-4216

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SARAH K VEE
08/24/2012

YELENA L MASLOV
08/27/2012

CAROL A HOLQUIST
08/27/2012

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: January 8, 2012

To: Amy Baird – Regulatory Project Manager
Division of Hematology Products (DHP)

From: Richard Lyght, Pharm.D. – Regulatory Review Officer
Division of Direct to Consumer Promotion (DCDP)
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP comments on draft pomalidomide tablets, for oral use Medication Guide

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This consult is in response to DHP's May 30, 2012 request for OPDP review of the draft pomalidomide Medication Guide. DCDP comments are based on the proposed draft marked-up labeling submitted by DMPP on December 21, 2012.

We have reviewed the comments made by DMPP and have no additional comments at this time.

OPDP appreciates the opportunity to provide comments. If you have any questions, please contact Richard Lyght at 301-796-2874 or at richard.lyght@fda.hhs.gov.

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/s/

RICHARD A LYGHT
01/09/2013