CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204026Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA	204026
Submission Date:	10 April 2012
Brand Name:	Pomalyst
Generic Name:	Pomalidomide
Formulation:	1, 2, 3, and 4 mg capsules
OCP Reviewers:	Rachelle M. Lubin, Pharm.D
OCP Team Leader:	Bahru A Habtemariam, Pharm.D
OCP Division:	Division of Clinical Pharmacology V
ORM Division:	Division of Drug Hematology Products
Applicant:	Celgene Corp.
Submission Type; Code:	Original NDA; 0000
Dosing regimen:	4 mg once daily on days 1-21 of repeated 28 day cycles (21/28 days) until disease progression
Indications	Multiple Myeloma

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1 EXECUTIVE SUMMARY

Pomalidomide, a derivative of thalidomide, is an immunomodulatory drug (IMiD), which is being developed as a capsule formulation for the treatment of multiple myeloma (MM). To support the New Drug Application submission, the applicant conducted several studies in healthy subjects and in patients.

To support the proposed indication, the sponsor conducted two pivotal studies in multiple myeloma patients. The first study (MM-002) compared pomalidomide alone vs. pomalidomide plus dexamethasone while the second study (IFM-2009-02) compared two dosing schedules where pomalidomide was administered either for 21 days of a 28 day treatment cycle or continuously for 28 days. The primary endpoint for study MM-002 was progression free survival (PFS) and response rate for study IFM-2009-02. For study MM-002, the median PFS was 10.7 weeks for the pomalidomide alone arm and 16.6 weeks for pomalidomide plus dexamethasone arm. For study IFM-200902, dose intensity had no effect; response rates where comparable at 35% and 34% for 21 and 28 day treatment schedules, respectively.

The human ADME properties of pomalidomide were evaluated following a single 2 mg radiolabeled dose in healthy subjects. It was determined that the predominant (~70%) circulating radioactive entity was pomalidomide. Pomalidomide is eliminated primarily through the kidneys (~ 73% of administered dose), with 2.2% of dose excreted as unchanged drug in urine. Approximately 15.5% of administered dose was excreted via the fecal route. Cytochrome P450 dependent metabolites accounted for 43% of the excreted radioactivity in humans. Circulating metabolites accounted for less than 10% of the total radioactivity. Pomalidomide is primarily metabolized by CYP3A4 and CYP1A2, with some contributions from CYP2C19 and CYP2D6.

The applicant conducted a food effect study to assess the influence of food on the PK of pomalidomide. However, the food effect study was conducted using a capsule formulation that failed to achieve bioequivalence with the to-be-marketed formulation. Therefore, the food effect study results were deemed unreliable to properly evaluate the effect of food on the PK of pomalidomide.

To date, population PK analysis, exposure-response analysis, organ impairment studies, and QT study results have not been submitted to the Agency for review.

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 has reviewed the information contained in NDA 204026. This NDA is considered incomplete from a clinical pharmacology perspective. The applicant will need to address the proposed PMRs.

1.2 Post Marketing Requirements

PMC or PMR	Key drug development question	Rationale
PMC ☒ PMR	Should pomalidomide dose be increased when taken with relevant CYP3A4 inducers? If so, by how much?	Pomalidomide is metabolized by CYP3A4. Information on the effect of induction was not submitted.
PMC ☒ PMR	Should pomalidomide dose be decreased when taken with relevant CYP3A4 inhibitors? If so, by how much?	Pomalidomide is metabolized by CYP3A4. Information on the effect of inhibition was not submitted.
☒ PMC PMR	Should pomalidomide dose be adjusted for patients who smoke? If so, by how much?	Pomalidomide is metabolized by CYP1A2. Information on the effect of induction was not submitted. PBPK modeling or in-vivo studies may be performed to determine the influence of CYP1A2 induction.
PMC ☒ PMR	Should pomalidomide dose be adjusted in hepatic impaired patients? If so, by how much?	Pomalidomide undergoes metabolism, but PK in hepatic impaired patients has not been assessed.
PMC ☒ PMR	Should pomalidomide dose be adjusted in renal impaired patients? If so, by how much?	Pomalidomide is excreted via the kidneys, but PK in renally impaired patients has not been assessed.
PMC ☒ PMR	Does pomalidomide cause QT interval prolongation?	Studies to assess the QT prolongation potential of pomalidomide have not been performed.
PMC ☒ PMR	Does food alter the pharmacokinetics of pomalidomide?	Studies to assess the effect of food on pomalidomide (final market formulation) exposure have not been performed.

Signatures:

Reviewer: Rachelle M. Lubin, Pharm.D.
Division of Clinical Pharmacology 5

Acting Team Leader: Bahru A. Habtemariam, Pharm.D.
Division of Clinical Pharmacology 5

Cc: DDOP: CSO - **A Baird;** MTL - **A Deisseroth**; MO - **S Ayache**
DCP-5: Reviewers - **R Lubin**, TL - **B Habtemariam**,
DDD - **B Booth;** DD - **A Rahman**

1.3 Summary of Important Clinical Pharmacology Findings

Pomalidomide is an immunomodulatory agent (derivative of thalidomide) with antiangiogenic and antineoplastic properties. Pomalidomide is being developed for the treatment of multiple myeloma (MM) patients who have received at least two prior therapies including bortezomib (b) (4) and have demonstrated disease progression on or within 60 days of completion of the last therapy. The applicant completed seven clinical pharmacology studies (Phase 1 and Phase 2) in healthy subjects and relapsed or refractory MM patients to evaluate the safety, pharmacokinetics, and efficacy of pomalidomide.

To support the proposed indication, the sponsor conducted two pivotal studies. The first study (MM-002) compared pomalidomide alone vs. pomalidomide plus dexamethasone in multiple myeloma patients. The second study (IFM-2009-02) compared two dosing schedules where pomalidomide was administered either for 21 days of a 28 day treatment cycle or continuously for 28 days. The primary endpoint was progression free survival (PFS) for study MM-002 and response rate in study IFM-2009-02. For study MM-002, the median PFS was 10.7 weeks for the pomalidomide alone arm and 16.6 weeks for pomalidomide plus dexamethasone arm. For study IFM-200902, dose intensity had no effect; response rates where comparable at 35% and 34% for the 21 and 28 day treatment schedules, respectively.

In MM patients, the peak concentrations (C_{max}) of pomalidomide were observed approximately 2 to 3 hours post dose. AUC was approximately dose-proportional, while C_{max} was less than dose-proportional. Half-life ranged from approximately 6 to 11 hours. After administration of radiolabeled pomalidomide (2 mg oral suspension), unchanged pomalidomide accounted for approximately 61.9% - 75.2% of circulating total radioactivity in plasma. Approximately 73% of the radiolabeled dose was recovered in the urine and 15.5% of dose was recovered in the feces. Excretion of unchanged pomalidomide accounted for approximately 10% (2.2% in urine and 7.7% in feces). In plasma, metabolites represented less < 10% of the total circulating radioactivity. Cytochrome P450 dependent metabolites account for approximately 43% of the total excreted radioactivity, while non-CYP dependent hydrolytic metabolites accounted for 25%. Pomalidomide was metabolized by CYP1A2, CYP3A4, CYP2C19, and CYPD6 at relative contributions of 54%, 30%, 11%, and 4%. Pomalidomide was found to be a substrate of P-glycoprotein (P-gp).

In-vitro findings show that pomalidomide had little or no inhibition on CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5 enzymes. The IC50 values for each CYP enzyme were greater than the highest concentrations measured (30 uM). Pomalidomide did not appear to induce ($\leq$1.3-fold increase) CYP enzymes 1A2, 2B6, 2C9, 2C19, and 3A4/5.

Although the applicant conducted a food effect study, the study was conducted using a test formulation that failed to meet FDA bioequivalence criteria to the final market formulation (reference). Results of the food effect study are deemed unreliable. The sponsor will be asked to conduct a formal food effect study using the commercial product as a post marketing requirement.

2 QUESTION BASED REVIEW

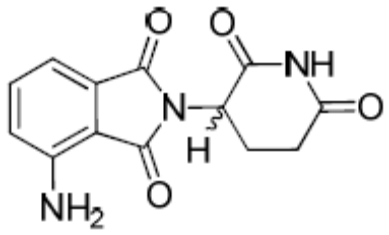
2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Pomalidomide is a thalidomide derivative (immunomodulatory agent) with antiangiogenic and antineoplastic properties.

Physico-chemical properties

- Structural formula:



- Established name: Pomalidomide
- Molecular Weight: 273.24
- Molecular Formula: $C_{13}H_{11}N_3O_4$
- Chemical Name: (RS)-4-Amino-2-(2,6-dioxo-piperidin-3-yl)-isoindoline-1,3-dione

Pomalidomide is a chiral molecule that contains a racemic mixture of the S-enantiomer and R-enantiomer (b) (4)

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Pomalidomide, an analogue of thalidomide, is an immunomodulatory agent with antineoplastic activity. In *in-vitro* cellular assays, pomalidomide inhibited proliferation and induced apoptosis of hematopoietic tumor cells. Additionally, pomalidomide inhibited the proliferation of lenalidomide-resistant multiple myeloma cell lines and synergized with dexamethasone in both lenalidomide-sensitive and lenalidomide-resistant cell lines to induce tumor cell apoptosis. Pomalidomide enhanced T cell- and natural killer (NK) cell-mediated immunity and inhibited production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes Pomalidomide demonstrated anti-angiogenic activity in a mouse tumor model and in *in-vitro* umbilical cord model.

The proposed pomalidomide indication is for patients with multiple myeloma who have received at least two prior therapies including bortezomib (b) (4) and have demonstrated disease progression on or within 60 days of completion of the last therapy.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The proposed dosing regimen for pomalidomide is 4 mg per day taken orally on days 1-21 of a 28 day treatment cycle. (b) (4) Treatment is continued until unacceptable toxicity or disease progression.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Seven studies assessing the PK, safety, and efficacy characteristics of pomalidomide were submitted by the applicant. Five Phase 1 studies were performed in healthy subjects, while two Phase 1b/2 studies were performed in MM patients (**Table 1**). The primary efficacy studies (MM-002 and IFM-2009-02) were conducted in MM patients.

Table 1: Studies supporting the clinical pharmacology and biopharmaceutics of pomalidomide (POM)

Study	Study Objective(s)	Study Design	Study population	Pomalidomide (POM) Total Daily Dose	# Subjects (Enrolled/ Completed with PK)
CP-005	BE and food effect	2-way crossover	HV	2 mg POM	28/28
CP-007	BE	2-way crossover	HV	1, 2, 3, and 4 mg POM	72/72
CP-004	Human ADME	Single-dose	HV	2 mg oral suspension POM	8/8
1398/132	Single-dose PK	Ascending single-dose	HV	1, 5, 10, 25, and 50 mg POM	30/20
CP-006	Multiple-dose PK	Ascending multiple-dose	HV	0.5, 1, 2 mg POM	33/24
MM-001	MTD determination	Open-label, ascending dose	R/R MM	1, 2, 5, 10 mg QD; 5 mg QOD	45/28
MM-002 (Phase1 & 2)	Phase 1: MTD Phase 2: Efficacy of POM alone and plus DEX	Open-label	R/R MM	MTD on days 1-21; DEX on days 1, 8, 15, 22 Q cycle	259/14
IFM-2009	Efficacy of two regimens	Open-label	R/R MM	4 mg POM + DEX	No PK

Dexamethasone (DEX)= 40 mg dose; ADME= Absorption, Distribution, Metabolism, Elimination; MTD= Maximum Tolerated Dose; HV=Healthy Volunteers, R/R= Relapsed/Refractory, QD = Once daily, QOD = Every other day

Primary Efficacy Studies:

Study MM-002 was a Phase 1/2, randomized, open-label, dose-escalation study to determine the maximum tolerated dose (MTD) and evaluate the safety and efficacy of pomalidomide alone and in combination with low dose dexamethasone in relapsed or refractory MM patients who have received prior treatment that includes lenalidomide and bortezomib. This study consisted of a single-agent (pomalidomide) dose-finding (3+3 design) Phase 1 part (n=38) and a randomized (pomalidomide alone vs. pomalidomide plus dexamethasone) Phase 2 part (n=221). In part 1, dosing cohorts were enrolled sequentially at dose levels of 2, 3, 4, 5, 6, 8, 10, and 12 mg of pomalidomide. Pomalidomide was administered once daily on days 1 to 21 of each 28 day cycle. In the combination treatment arm, the starting dose of dexamethasone was 40 mg (for

patients ≤ 75 years) or 20 mg (for subjects > 75 years) on days 1, 8, 15, and 22 of each 28 day cycle. The MTD was found to be 4 mg per day in the Phase 1 part of the study.

The MTD determined in the phase 1 part of the study (4 mg daily) was used for the phase 2 part of the study. Median progression free survival (PFS), the primary endpoint, was 10.7 weeks and 16.6 weeks following treatment with pomalidomide alone and pomalidomide plus dexamethasone, respectively. Forty-five patients remained on treatment as of the data cutoff (April 1, 2011).

During the Phase 2 portion of this study, PK data were collected from a subset of relapsed/refractory MM patients (n=14). The MTD (4 mg daily) determined from the Phase 1 segment of this study was used as the starting dose for the Phase 2 segment. AUC_{0-t} and C_{max} for pomalidomide plus dexamethasone and pomalidomide alone arms were similar on day 1 and day 8.

Study IFM 2009-02 (non-applicant) was a randomized (n=84), open-label study to evaluate the safety and efficacy of two regimens (21/28 days vs. 28/28 days) of oral 4 mg pomalidomide in combination with low dose 40 mg dexamethasone in relapsed/refractory MM patients who were progressive and received prior treatment with lenalidomide and bortezomib. The primary endpoint, response rate (PR+CR), was approximately 34.9% and 34.1% in patients who received pomalidomide plus dexamethasone for 21 days out of a 28 day treatment cycle and 28 days out of a 28 day treatment cycle, respectively. As of March 1, 2011, a total of 23 patients remain in the study.

Supportive Studies (Applicant conducted):

Study MM-001 was a Phase 1b study (n=45) in relapsed or refractory MM patients to determine the MTD and preliminary efficacy of pomalidomide. Pomalidomide doses between 1 – 10 mg QD (Cohort 1) and 1 – 10 QOD (Cohort 2) were given to patients. Approximately 54% of patients had a response that included: 17% of patients with complete response (CR), 13% of patients with a very good partial response (VGPR), and 25% of patients with a PR. Median PFS was 9.75 months and median overall survival (OS) was 22.5 months. In cohort 2, approximately 10% of patients had a CR, 29% had a VGPR, and 10% of patients had a PR. PFS was 10.5 months and median OS was 33 months.

The MTD was determined to be 2 mg once daily or 5 mg every other day in Cohort 1 and Cohort 2, respectively. $AUC_{0-\infty}$ and C_{max} was less than dose-proportional over the dose range of 1 to 10 mg on day 1 and at week 4 for the 1 to 5 mg dose range.

Clinical Pharmacology Studies: There are a total of seven clinical studies completed that provide PK characteristics of pomalidomide.

Study CP-005 was a Phase 1, 3-period, 2-way crossover study to evaluate the bioequivalence (BE) of a new formulation (test) of the 2 mg capsule compared to the reference 2 mg capsule formulation. A secondary objective was to evaluate the effect of food on the PK of the 2 mg test capsule formulation. Results show that the 2 mg test formulation was not BE to the 2 mg reference formulation. C_{max} was (b) (4) for test formulation compared to reference formulation (b) (4) A food effect arm was added to evaluate the influence of a high fat meal on the PK of the 2 mg test formulation. Pomalidomide exposure (b) (4) (C_{max}: by (b) (4), AUC: by (b) (4) in the presence of food. Since the food effect was conducted using a formulation that was found to be not BE to the final market formulation, the food effect portion of the PK data were deemed unreliable to determine the effect of food on the exposure of pomalidomide.

Study CP-007 was a Phase 1, open-label, randomized, 2-period, 2-way crossover BE study (n=36) to compare the 1 mg and 2 mg reference formulations to the 3 mg and 4 mg test formulations. Results show that the 3 mg and 4 mg test formulations were BE to the 1 mg and 2 mg reference formulations based on the FDAs 80 – 125% criteria for AUC and C_{max}.

Study 1398/132 was a single-arm, placebo-controlled, ascending single-dose study to assess safety, PK and PD in healthy subjects (n=30). Subjects received pomalidomide doses at 1, 5, 10, 25, and 50 mg. Peak concentrations were observed at 2.5 to 6 hours post-dose. AUC increased approximately in a dose-proportional manner and C_{max} increased in a less than dose-proportional manner. Half-life of pomalidomide was between 8.2 – 10.8 hours.

Study CP-004 was an open-label mass balance study to assess the absorption, metabolism and excretion of a single 2 mg oral suspension dose (100 uCi) of [^{14}C]-pomalidomide. Unchanged pomalidomide accounted for 61.9% to 75.2% of circulating total radioactivity exposure. Approximately 73% of radiolabeled pomalidomide was recovered in the urine and 15.5% in feces. Unchanged pomalidomide accounted for 2.2% and 7.7% in urine and feces, respectively. T_{max} for pomalidomide and total radioactivity in plasma and whole blood was observed at 2.5 to 3.25 hours. Metabolite exposure was < 10% of total radioactive or pomalidomide in plasma.

Study CP-006 was a randomized, placebo-controlled, multiple ascending dose study performed in healthy male subjects to evaluate the safety and PK of pomalidomide (0.5, 1, 2 mg dose). Maximum concentrations were observed between 1.5 to 2.25 hours post-dose. Pomalidomide AUC and C_{max} were approximately dose-proportional within the dose range studied. Up to 14% accumulation on day 5 compared to day 1 was observed for C_{max} and AUC_{0-24}. Half-life was approximately 6 hours and pomalidomide Cmin reached steady state by day 3 at all dose levels. Pomalidomide is distributed in the semen of healthy subjects at a concentration approximately 67% of plasma concentrations at 4 hours post-dose.

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

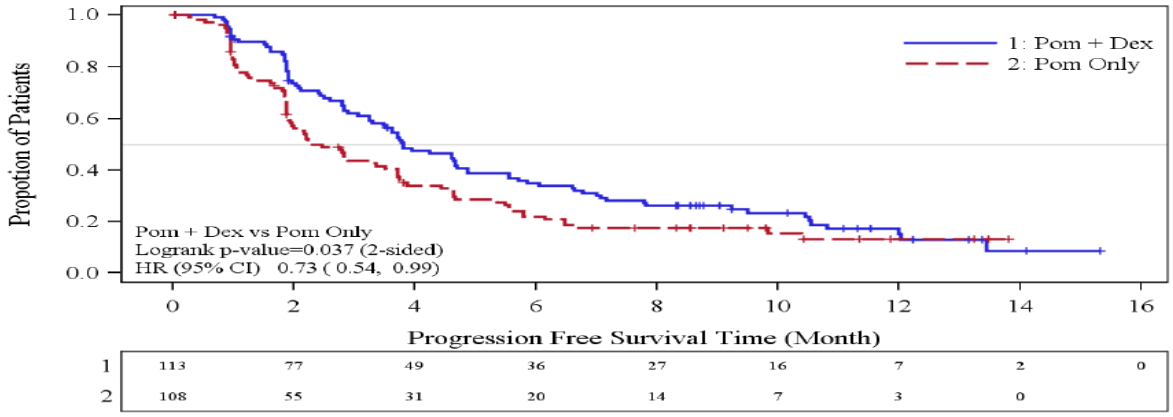
Efficacy claims are based on two primary studies conducted in relapsed or refractory MM patients: study MM-002 and study IFM 2009-02.

Study MM-002 (Phase 2): A total of 221 patients were enrolled in the trial, 113 patients in the pomalidomide plus dexamethasone arm and 108 patients in the pomalidomide alone arm (**Table 2**). Theses patients had received prior treatment with lenalidomide and bortezomib. The median age of the study population was 63 years (range: 34 – 88 years). The primary endpoint for study MM-002 was PFS. The median PFS in patients treated with pomalidomide plus dexamethasone was 16.6 weeks (**Table 2**). For those treated with pomalidomide alone, the median PFS was 10.7 weeks (**Table 2**).

Table 2: Summary of Efficacy Endpoints in Study MM-002

	Pom + Dex (N=113)	**Pom (N=108)**
Median PFS (weeks) (95% CI)	16.6 (14.1, 21.1)	10.7 (8.3, 16.1)
Hazard ratio (95% CI)	0.73 (0.54, 0.99)	
Pomalidomide (Pom); Dexamethasone (Dex)		

Figure 1 (applicant provided): PFS of Pomalidomide (+/- Dexamethasone) in Study MM-002



Dex = dexamethasone; EBMT = European Group for Blood and Marrow Transplantation; HR = hazard ratio; IRAC = Independent Response Adjudication Committee; ITT = Intent to treat; Pom = pomalidomide

Source: CC-4047-MM-002 Figure 14.2.1.1
Cutoff date: 01 Apr 2011

Figure generated by applicant.

Study IFM 2009-02: The trial enrolled a total of 84 patients with multiple myeloma. Most subjects were males (68%) and the median age was 60 years old (range: 42 – 83 years). Patients received 4 mg of pomalidomide plus low dose dexamethasone. In this study, the treatment intensity (21 out of 28 days vs. 28 out of 28 days) was evaluated. The overall response rate (primary endpoint) was approximately 35% vs. 34%, which was similar regardless of the intensity of the treatment (21/28 days vs. 28/28 days) with pomalidomide plus dexamethasone (**Table 3**). Response rates of the two treatment regimens are shown in **Table 3**.

Table 3: Summary of Efficacy Endpoints in Study IFM 2009-02

	Pom (21/28) + Dex (N=43)	**Pom (28/28) +Dex (N=41)**
Overall response rate (CR + PR), n (%)	15 (34.9)	14 (34.1)
Complete Response (CR), n (%)	1 (2.3)	2 (4.9)
Partial Response (PR), n (%)	14 (32.6)	12 (29.2)

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Pomalidomide was measured in plasma, urine and semen. Pomalidomide has multiple metabolites (6 detected by radiochromatography) in plasma, all of which were < 10% relative to parent or total radioactivity. No validated analytical methods were developed to quantify metabolites.

2.2.4 Exposure-Response

No exposure-response analysis was conducted.

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

Because PK samples were collected in a small number of patients (n=14) that took part in the efficacy trial (MM-002), exposure-response analyses could not be conducted.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

Clinical studies assessing the relationship between exposure and safety were not performed due to limited collection of PK samples in MM patients.

2.2.4.3 Does this drug prolong the QT or QTc interval?

A study designed to assess the QT interval prolongation potential of pomalidomide was not performed. The applicant plans on conducting a thorough QT study.

ECG/QT data obtained from combined phase 1 studies reported that changes in QRS complex appeared to be random in all dose groups without a drug or dose related pattern; however, overall, there were more subjects with prolonged or borderline QTc prolongation across the daily dosing groups.

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

There were no sufficient PK and response data to conduct dose-concentration-response analyses.

2.2.5 What are the PK characteristics of the drug and its major metabolite?

2.2.5.1 What are the single dose and multiple dose PK parameters?

Following single oral doses of pomalidomide, ranging from 0.5 to 10 mg, in healthy subjects, AUC increased in an approximately dose-proportional manner, while C_{max} increased in a less than dose-proportional manner over the dose range of 1 to 50 mg (**Table 4**). Maximum concentrations were observed between 1.75 hours and 3.25 hours post-dose. AUC and Cmax following multiple-doses of pomalidomide were approximately dose-proportional. Pomalidomide reached steady state by day 3. The mean half-life ranged from approximately 6 – 10 hours.

A total of eight metabolites were detected following a single radiolabeled dose of pomalidomide. Six of those metabolites were detected with radiochromatography. Metabolites exposures were < 10% of plasma total radioactive pomalidomide exposure. Median T_{max} for detected metabolites ranged from 1 – 6 hours, with a mean half-life of 9 – 13 hours. **Table 4** summarizes the PK of single oral doses of pomalidomide.

Table 4: PK Parameters of Pomalidomide in Plasma Following Single Oral Doses in Healthy Subjects

Parameter	Geometric Mean (CV%)								
	0.5 mg	1 mg		2 mg		3 mg	4 mg	5 mg	10mg
	CP-006	1398/132	CP-006	CP-005	CP-006	CP-007	CP-007	1398/132	1398/132
	(N=8)	(N=4)	(N=8)	(N=27)	(N=8)	(N=35)	(N=36)	(N=4)	(N=4)
$AUC_{(0\text{-}tz)}$ (ng*h/mL)	58.6[b] (24.5)	118 (17.7)	95.0[b] (35.4)	(b) (4)	232[b] (24.5)	353 (20.3)	476 (33.4)	516 (21.3)	911 (13.5)
$AUC_{(0\text{-}\infty)}$ (ng*h/mL)	NA	122 (17.3)	NA		NC	357 (20.2)	481 (33.6)	529 (21.5)	930 (14.0)
C_{max} (ng/mL)	6.73 (17.8)	11.2 (18.1)	13.1 (18.0)		28.5 (18.6)	42.2 (19.6)	58 (19.0)	51.8 (12.2)	80.8 (11.3)
t_{max}[a] (h)	1.75 (1.00-3.00)	3.00 (0.50-4.0)	1.76 (1.00-3.00)		2.25 (1.50-4.00)	2.00 (1.00-4.05)	2.00 (1.00-3.02)	2.50 (1.5-3.0)	3.25 (2.0-6.0)
$t_{1/2}$ (h)	NC	8.65 (14.6)	NC		NC	6.08 (18.7)	6.15 (24.7)	10.1 (14.2)	8.17 (33.7)
CL/F (L/hr)	NC	8.2 (17.3)	NC		NC	8.39 (20.2)	8.31 (33.6)	9.5 (21.5)	10.7 (14.0)
V_z/F (L)	NC	102 (21.8)	NC		NC	73.7 (19.9)	73.8 (20.1)	138 (29.9)	127 (32.0)

$AUC_{(0\text{-}tz)}$ = area under the plasma concentration-time curve from time zero up to the last quantifiable concentration; $AUC_{(0\text{-}\infty)}$ = area under the plasma concentration-time curve from time zero to infinity; C_{max} = maximum observed plasma concentration; CL/F = apparent total plasma clearance; CV = coefficient of variation; N = Number of subjects; NA = not applicable; NC = not calculable; $t_{1/2}$ = terminal elimination half life; t_{max} = time to maximum observed plasma concentration; V_z/F = apparent volume of distribution during the terminal phase

Data from Studies 1398/132, CC-4047-CP-005, CC-4047-CP-006, CC-4047-CP-007

[a] Median (min, max)

[b] $AUC_{(0\text{–}24)}$ (area under the plasma concentration-time curve from time zero to 24 hours post dose)

Table generated by applicant.

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

To compare the PK of pomalidomide in healthy subjects and MM patients, multiple inter-study comparisons were conducted. Overall, pomalidomide showed comparable PK between healthy subjects and MM patients (**Tables 5**). PK data for healthy subjects were available from study CP-007, and data for MM patients were obtained from study MM-002.

Table 5: PK Parameters of Pomalidomide in Plasma Following Single Oral dose of 4 mg to Healthy Male Subjects and Relapsed or Refractory Multiple Myeloma Patients

Parameter	Geometric Mean (CV%)	
	Healthy Subjects	Subjects with Relapsed or Refractory MM
	4 mg QD	4 mg QD
	Day 1 (N=36)	Day 1 (N=7)
$AUC_{(0-24)}$ (ng*h/mL)	476 (33.4)	300 (39.9)
$AUC_{(0-\infty)}$ (ng*h/mL)	481 (33.6)	NC
C_{max} (ng/mL)	57.8 (19.0)	62.4 (28.1)
t_{max}[a] (h)	2.00 (1.00-3.02)	2.00 (1.00-3.00)
$t_{1/2}$ (h)	6.15 (24.7)	NC
CL/F (mL/min)	8.31 (33.6)	NC
V_z/F (L)	73.8 (20.1)	NC

$AUC_{(0-24)}$ = area under the plasma concentration-time curve from time zero up to 24 hours; Cmax = maximum observed plasma concentration; CL/F = apparent total plasma clearance; CV = coefficient of variation; N = Number of subjects; NC = Not calculable; OD = daily; QD = once daily; $t_{1/2}$ = terminal elimination half-life; t_{max} = time to maximum observed plasma concentration; V_z/F = apparent volume of distribution during the terminal phase
Healthy subject data from CC-4047-CP-007 with PK sampling out to 48 hours; MM subject data from CC-4047-MM-002 Phase 2 with PK sampling out to 8 hours
[a] Median (min, max)

Table generated by applicant.

2.2.5.3 What are the characteristics of drug absorption?

Following 2 mg (suspension) of [^{14}C]-pomalidomide in healthy subjects, approximately 70% of radiolabeled dose was absorbed. Median T_{max} was approximately between 2 and 3 hours. The absolute bioavailability of pomalidomide was not determined.

2.2.5.4 What are the characteristics of drug distribution?

Protein Binding

The protein binding properties of pomalidomide was investigated in an *in-vitro* study (DMPK-015) using pomalidomide (racemate) concentrations of 30, 100, 300, 1000, and 3000 ng/mL. At all concentrations, plasma protein binding for R-enantiomer and S-enantiomer was between 11.9 – 24.8% (mean: 15.8%) and 40.1 – 43.9% (mean: 42.2%), respectively. Mean apparent volume of distribution of pomalidomide ranged from 62 – 138 L and 65 – 97 L for healthy subjects and MM patients, respectively (**Table 5** in Section 2.2.5.2).

Blood/Plasma Ratio

The extent of blood partitioning of pomalidomide was determined in the mass balance study (CP-004). Blood to plasma ratios for radioactivity ranged from 0.749 to 0.904, following 0.5 to 24 hours post-dose, respectively.

Semen Distribution

Pomalidomide is distributed in the semen of healthy male subjects at a concentration approximately 67% of plasma concentrations at 4 hours post-dose.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

In study CP-004, eight healthy male subjects received a single 2 mg oral suspension dose containing 100 uCi of [^{14}C]-pomalidomide. Approximately 72.8% of the radiolabeled pomalidomide dose was recovered in the urine, while 15.5% was recovered in the feces (**Table 6**). Unchanged pomalidomide accounted for 2.2% and 7.7% of the dose in urine and feces, respectively. Pomalidomide and eight metabolites were identified in plasma following 2 mg of [^{14}-C] pomalidomide. Parent compound (unchanged) accounted for approximately 70% of circulating total radioactivity. Exposures of six metabolites, which were identified by radiochromatography, accounted for less than 10% of the total plasma radioactivity.

CYP450 dependent metabolites accounted for approximately 43% of the excreted radioactivity and non-CYP450 dependent hydrolytic metabolites accounted for 25%.

Table 6: Unchanged Pomalidomide (and metabolites) Characterized/Identified in Human Plasma, Urine, and Feces after a Single Oral Dose of 14-C Pomalidomide (2 mg) to Healthy Subjects

Metabolite Entity		Plasma[a] (as % of AUC TRA)	Excreted (% of Dose)		
			Urine[b]	Feces[b]	Total[b]
TRA	Total Radioactivity	100	72.1	15.3	87.4
Pomalidomide	Unchanged	69.6	2.17	7.72	9.89
M2 (3-aminophthalic acid)	N-dealkylation (loss of glutarimide ring)/hydrolysis/ hydrolytic deamination of CC-4047	1.71	1.44	ND	1.44
M10 (CC-15262)	Hydrolysis of CC-4047	ND	1.51	0.28	1.79
M11 (CC-8017)	Hydrolysis of CC-4047	6.34	23.3	0.33	23.6
M12	Glucuronide of M17	4.59	17.1	ND	17.1
M13	Glucuronide of M17	1.99	12.4	ND	12.4
M16	Hydroxylated	6.13	7.03	ND	7.03
M17	Hydroxylated	4.00	3.20	2.78	5.98
M18 (CC-4067)	N-acetylated	D	0.08	D	0.08
M19 (CC-12074)	Hydroxylated	D	D	ND	D

AUC = area under the plasma concentration-time curve; AUC_{0-24} = area under the plasma concentration-time curve from time 0 to 24 hours after administration of the study drug; AUC_{0-t} = area under the plasma concentration-time curve from time 0 to the time of the last measurable concentration; D = detected only by LC/MS, but could not be quantified; ND = not detected; TRA = total radioactive amount.

[a] Geometric mean %AUC values [AUC_{0-t} (unchanged drug or metabolite)/AUC_{0-24} (TRA) * 100%] from 8 subjects.

[b] Mean percent of dose in 0 to 72-hour urine and 0 to 96-hour fecal samples.

Table generated by applicant.

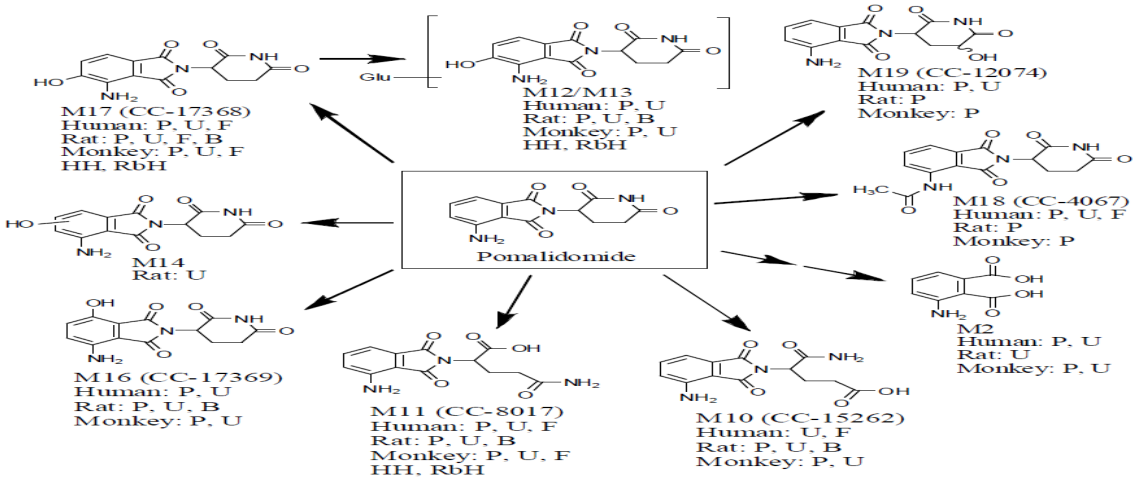
2.2.5.6 What are the characteristics of drug metabolism?

The *in-vitro* metabolism studies indicated that the major pathways for metabolism of pomalidomide included hydroxylation, followed by glucoronidation and hydrolysis.

Results from a mass balance study indicated that pomalidomide is metabolized to at least 8 metabolites (**Figure 2**) that are present in plasma, urine and feces (see **Table 6** is Section 2.2.5.5). Metabolites did not

exceed 10% of the total plasma radioactivity exposure. Metabolites were formed primarily by hydroxylation, followed by glucoronidation and hydrolysis of pomalidomide. Parent drug was the major circulating radioactive component (~70% of circulating radioactivity).

Figure 2: Propose Metabolic Pathways of Pomalidomide In-Vivo in Rats, Monkeys, and Humans and *In-Vitro* in Hepatocytes from Rabbits and Humans



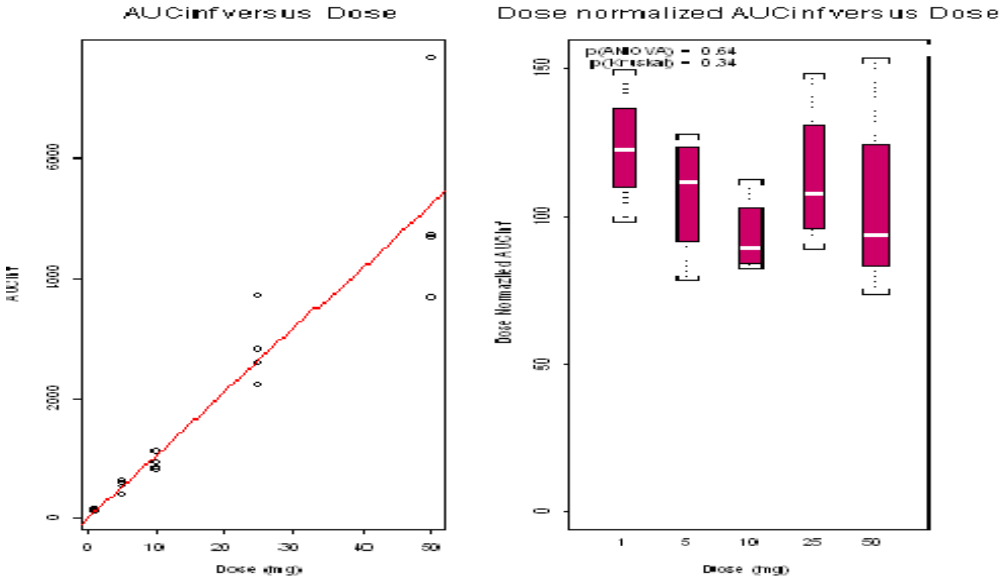
2.2.5.7 What are the characteristics of drug excretion?

Pomalidomide is mainly excreted via the kidneys. Over 216 hours following a 2 mg dose of [^{14}-C] pomalidomide in the mass balance study, the majority (72.8%) of the administered dose was recovered in the urine, while approximately 15.5% of the dose was recovered in the feces (over 96 hour period). Unchanged pomalidomide accounted for 2.2% and 7.7% of recovered dose in urine and feces, respectively. The major metabolites in urine were M11, M12 and M13 and accounted for 23.3%, 17.1% and 12.4%, respectively. Additional, minor metabolites, M2, M10, M16, and M17 accounted for 1.44%, 1.51%, 7.03%, and 3.2% of dose, respectively. See **Table 6**, in section 2.2.5.5, for details on individual metabolite excretion results.

2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The dose proportionality of pomalidomide was assessed using data from two ascending dose studies in healthy subjects and MM patients. Following single oral doses (1, 5, 10, 25, and 50 mg) of pomalidomide in healthy subjects, AUC increased in a approximately dose-proportional manner, while C_{max} increased in a less than dose-proportional manner over the doses studied (study 1398/132; Exploratory ANOVA test: **Figure 3**). In MM patients (study MM-001); pomalidomide dose levels evaluated for PK included 1, 2, 5, and 10 mg once daily and 5 mg on alternate days. Exploratory analysis also showed that AUC increased in a dose-proportional manner and C_{max} was less than dose-proportional up to 5 mg. The applicant states that there was a dose-dependent decrease in the absorption rate in the dose range of 10 – 50 mg in healthy subjects.

Figure 3: Exploratory ANOVA Test on the Dose Normalized AUC_{inf} in Healthy Subjects (Study 1398/132)



2.2.5.9 How do the PK parameters change with time following chronic dosing?

Following multiple doses of 0.5, 1 and 2 mg of pomalidomide in healthy subjects (study CP-006), minimal accumulation of up to 14% was observed for AUC_{0-24} and C_{max} on day 5 compared to day 1. Similarly, modest accumulations were observed in study MM002, with an AUC_{0-t} and C_{max} at 27 – 31% and 17 – 22% higher on day 8 compared to day 1, respectively.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Following single doses of pomalidomide, inter-individual variability of pomalidomide AUC was between 13.5% to 39.4% and 20.5% to 55.4% in healthy subjects and MM patients, respectively. Intra-subject variability of AUC was estimated at approximately 10% in healthy subjects following single doses of pomalidomide. Variability for C_{max} ranged from 11.3% to 26.2% and 11.1% to 40.6% in healthy subjects and MM patients, respectively. Overall, higher inter-subject variability was observed in MM patients.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

It is not known which intrinsic factors influence exposure and/or response properties of pomalidomide. The sponsor did not conduct organ impairment studies, population PK or exposure-response analyses.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups?

The applicant has not performed formal exposure-response or population PK analyses. Results in sections 2.3.2.1, 2.3.2.2 and 2.3.2.3 are from visual assessment and exploratory covariate analysis performed using PK data in MM patients (studies MM-001 and MM-002).

2.3.2.1 Body Weight

Exploratory analysis show that there was no notable relationship between body weight (range: 48-94.5 kg) and pomalidomide exposure (**Figure 4**). Formal population PK analysis will still need to be performed.

Figure 4: Effect of Body Weight on Pomalidomide Exposure in MM Subjects (Exploratory Analysis)

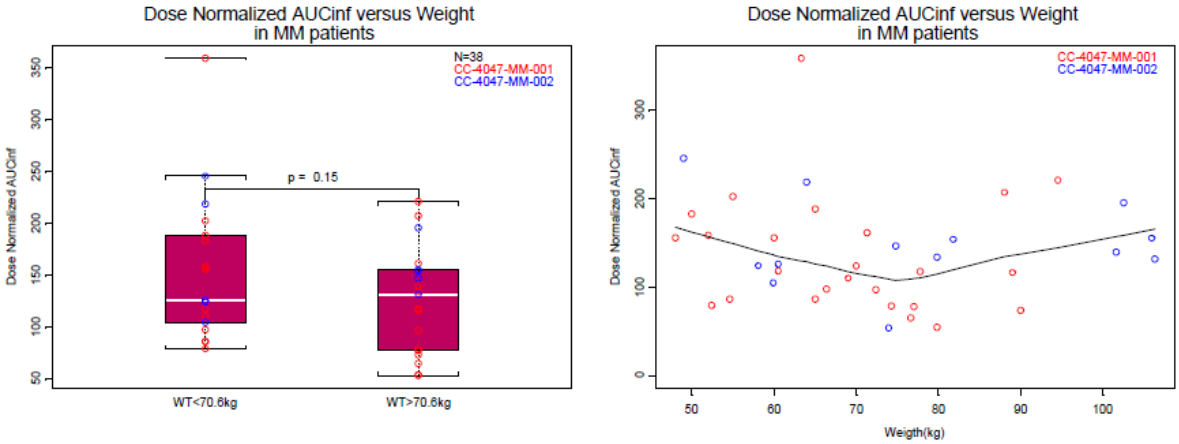


Figure generated by applicant.

2.3.2.2 Gender

Exploratory analysis shows that there was no notable relationship between gender and pomalidomide AUC_{inf} (**Figure 5**). Formal population PK analysis will still need to be performed.

Figure 5: Effect of Gender on Pomalidomide Exposure in MM Subjects (Exploratory Analysis)

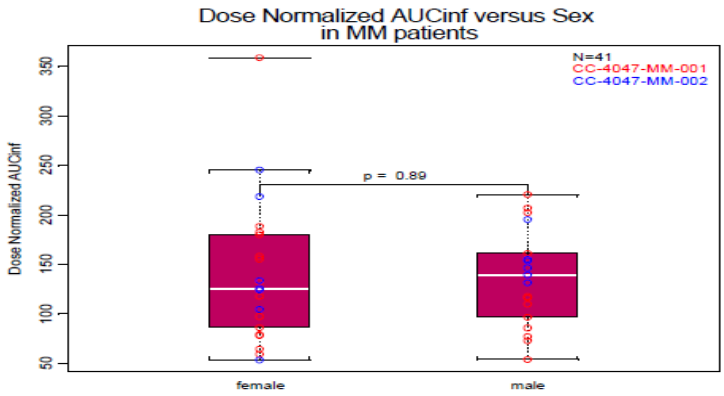


Figure generated by applicant.

2.3.2.3 Pediatric Population

Studies have not been conducted in pediatric patients.

2.3.2.4 Age

The applicant claims that there was no notable relationship between age (range: 48 – 65 years) and pomalidomide AUC_{inf} (**Figure 6**). Formal population PK analysis will still need to be performed.

Figure 6: Effect of Age on Pomalidomide Exposure in MM Subjects (Exploratory Analysis)

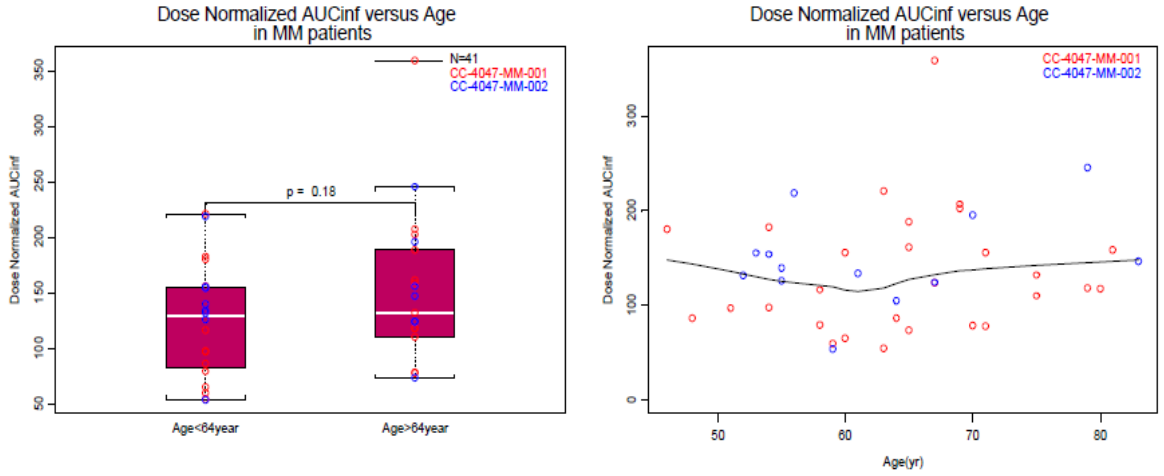


Figure generated by applicant.

2.3.2.5 Renal impairment

Based on the mass balance study, approximately 73% of radiolabeled pomalidomide was excreted via the kidneys. To date, the applicant has not completed a renal impairment study. The applicant states that a renal impairment study (MM-008) is ongoing and will be completed on 5 June 2017. It was noted that primary efficacy studies (MM-002 and IFM 2009-02) excluded patients with a serum creatinine > 3 mg/dL, CrCL > 50 mL/min (IFM-2009-02 only).

2.3.2.6 Hepatic impairment

Based on the *in-vitro* studies, pomalidomide is metabolized primarily by CYP3A4 and CYP1A2, therefore hepatic impairments studies will need to be conducted. The applicant plans to conduct a hepatic impairment study in the first quarter of 2013. Thus far, the PK of pomalidomide was not evaluated in patients with hepatic impairment. Of note, primary efficacy studies excluded patients with a liver transaminases > 3 x ULN and serum total bilirubin > 2 mg/dL.

2.3.2.7 What pregnancy and lactation use information is there in the application?

Non-clinical study results show that pomalidomide is teratogenic. Pomalidomide concentrations crossed the placenta and were detected in the fetal blood of animals. Pomalidomide was also detected in milk of lactating

animals (milk:plasma ratio was 0.63 to 1.5).

2.3.2.8 Does genetic variation impact exposure and/or response?

The applicant has not assessed the impact of genetic factors on exposure and /or response to pomalidomide.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

The applicant did not conduct a popPK or exposure-response analysis.

2.4.2 Drug-drug interactions

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Yes. See below.

2.4.2.2 Is the drug a substrate of CYP enzymes?

An *in-vitro* study (DMPK-22) showed that the major enzymes involved in the metabolism of pomalidomide were CYP3A4 and CYP1A2, with some contribution from CYP2C19 and CYP2D6. Therefore inhibitors and inducers of these CYP enzymes could affect the PK of pomalidomide.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

***In-vitro* CYP inhibition**

In-vitro studies with pomalidomide were conducted to assess the potential for pomalidomide to inhibit CYP450 enzymes. Pomalidomide was evaluated for its ability to inhibit the CYP enzymes directly or in a time-dependent manner. The enzymatic metabolic activities of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5 were investigated in human liver microsomes (pool of 16 samples) in the presence and absence of pomalidomide (concentration range: 0 – 30 uM).

Results of the *in-vitro* CYP450 inhibition study (DMPK-024) showed that pomalidomide had little or no inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5 enzymes. The IC50 values for each CYP enzyme was greater than the highest concentrations measured (30 uM). The applicant states that the mean C_{max} value following multiple-daily doses of 4 mg (clinical dose) pomalidomide in MM patients was approximately 80 ng/mL (0.3 uM) (study MM-002). Therefore the C_{max} /IC50 ratio for all measured CYP enzymes (IC50 values > 30 uM) would be 0.02, which is less than 0.1, for both direct inhibition and time dependent inhibition. Listed in **Table 7**, is a summary of the IC50 values for the measured CYP interaction.

Table 7: *In-Vitro* Evaluation of CC-4047 (Pomalidomide) as an Inhibitor of Human CYP Enzymes.

Enzyme	CYP Reaction	Direct inhibition		Time-dependent inhibition	
		Zero-minute pre-incubation		30-minute pre-incubation	
		IC_{50} (µM)	Maximum inhibition at 30 µM (%) [a]	IC_{50} (µM)	Maximum inhibition at 30 µM (%) [a]
CYP1A2	Phenacetin *O*-deethylation	>30	NA	>30	NA
CYP2A6	Coumarin 7-hydroxylation	>30	NA	ND	ND
CYP2B6	Bupropion hydroxylation	>30	3.7	ND	ND
CYP2C8	Paclitaxel 6α-hydroxylation	>30	NA	ND	ND
CYP2C9	Diclofenac 4′-hydroxylation	>30	NA	>30	NA
CYP2C19	*S*-Mephenytoin 4′-hydroxylation	>30	NA	>30	NA
CYP2D6	Dextromethorphan *O*-demethylation	>30	NA	>30	NA
CYP2E1	Chlorzoxazone 6-hydroxylation	>30	NA	ND	ND
CYP3A4/5	Testosterone 6β-hydroxylation	>30	6.9	>30	12
CYP3A4/5	Midazolam 1′-hydroxylation	>30	NA	>30	2.3

Notes Average data (i.e., percent of control activity) obtained from duplicate samples for each test article concentration were used to calculate IC_{50} values. IC_{50} values were calculated with XLfit.

[a] Maximum inhibition (%) is calculated with the following formula and data for the highest concentration of test article for which usable data were collected (results are rounded to two significant figures): Maximum inhibition (%) = 100% – Percent solvent control.

[b] Time-dependent inhibition was determined by comparison of IC_{50} values with and without pre-incubation, by comparison of the maximum inhibition (%) with and without pre-incubation and by visual inspection of the IC_{50} plot.

ND Not determined. Time-dependent inhibition was not determined for these enzymes.

NA Not applicable. Inhibition was not observed at the highest concentration of CC-4047 evaluated (30 µM).

***In-vitro* CYP induction**

The potential of pomalidomide (0.3, 1 and 3 uM) to induce CYP enzymes 1A2, 2B6, 2C9, 2C19, and 3A4/5 was evaluated in an *in-vitro* study. Induction was evaluated by catalytic activity. Positive controls included omeprazole (100 uM), phenobarbital (750 uM) and rifampin (10 uM) and probe substrates included phenacetin (CYP1A2), bupropion (CYP2B6), diclofenac (CYP2C9), S-mephenytoin (CYP2C19), and testosterone (CYP3A4/5). Treatment of cultured human hepatocytes with pomalidomide (up to 3 uM) BID for three consecutive days, had little or no effect (≤1.3-fold increase) on the activity of any of the CYP enzymes measured. Listed in **Table 8** and **Table 9** are the enzyme activities and fold increases following the incubation of pomalidomide with probe CYP450 substrates.

Table 8: Effects of Treating Cultured Human Hepatocytes with CC-4047 (Pomalidomide) or Prototypical Inducers on the Activity of Microsomal CYP450 Enzymes

Treatment	Concentration	Enzymatic activity (pmol/mg microsomal protein/min) [a]				
		Phenacetin *O*-dealkylation (CYP1A2)	Bupropion hydroxylation (CYP2B6)	Diclofenac 4′-hydroxylation (CYP2C9)	*S*-Mephenytoin 4′-hydroxylation (CYP2C19)	Testosterone 6β-hydroxylation (CYP3A4/5)
Dimethyl sulfoxide	0.1% (v/v)	44.8 ± 1.1	25.7 ± 7.5	1200 ± 150	5.82 ± 1.53	3360 ± 2040
CC-4047	0.3 µM	48.0 ± 2.0	26.4 ± 7.7	1370 ± 110	6.56 ± 1.15	3870 ± 2180
CC-4047	1 µM	35.9 ± 8.1	23.0 ± 11.1	1250 ± 250	5.61 ± 1.92	3480 ± 2390
CC-4047	3 µM	43.5 ± 2.8	23.9 ± 6.9	1350 ± 90	6.17 ± 0.73	4240 ± 2500
Omeprazole	100 µM	1300 ± 700	143 ± 114	1920 ± 420	8.76 ± 4.34	5110 ± 2390
Phenobarbital	750 µM	100 ± 32	169 ± 149	1790 ± 750	12.9 ± 9.5	13800 ± 6400
Rifampin	10 µM	83.5 ± 25.2	140 ± 93	2850 ± 790	67.1 ± 42.5	16300 ± 4200

a Values are the mean ± standard deviation of three determinations (human hepatocyte preparations H719, H723 and H724).

Table 9: Effects of Treating Cultured Human Hepatocytes with CC-4047 (Pomalidomide) or Prototypical Inducers on the Activity of Microsomal CYP450 Enzymes: Fold Increase

Treatment	Concentration	Fold increase [a]				
		Phenacetin *O*-dealkylation (CYP1A2)* §	Bupropion hydroxylation (CYP2B6)*	Diclofenac 4′-hydroxylation (CYP2C9)	*S*-Mephenytoin 4′-hydroxylation (CYP2C19)	Testosterone 6β-hydroxylation (CYP3A4/5) ∞
Dimethyl sulfoxide	0.1% (v/v)	1.00 ± 0.02	1.00 ± 0.29	1.00 ± 0.13	1.00 ± 0.26	1.00 ± 0.61
CC-4047	0.3 µM	1.07 ± 0.03	1.04 ± 0.08	1.15 ± 0.08	1.15 ± 0.13	1.20 ± 0.14
CC-4047	1 µM	0.798 ± 0.165	0.860 ± 0.200	1.03 ± 0.13	0.951 ± 0.100	0.961 ± 0.201
CC-4047	3 µM	0.972 ± 0.084	0.931 ± 0.020	1.13 ± 0.08	1.09 ± 0.15	1.30 ± 0.12
Omeprazole	100 µM	28.9 ± 15.1	5.28 ± 3.07	1.61 ± 0.36 †	1.51 ± 0.72	2.04 ± 1.55
Phenobarbital	750 µM	2.22 ± 0.67	5.86 ± 4.26	1.46 ± 0.42	2.05 ± 0.97	4.90 ± 2.31 †
Rifampin	10 µM	1.87 ± 0.59	5.31 ± 2.40	2.40 ± 0.76 †	12.5 ± 10.1 †	6.80 ± 5.27 †

a Values are the mean ± standard deviation of three determinates (human hepatocyte preparations H719, H723 and H724). Fold increase is rounded to three significant figures and the corresponding standard deviation is rounded to the same degree of accuracy.
† Significantly different from 0.1% dimethyl sulfoxide, (v/v) according to Dunnett's Method ($p < 0.05$) with positive controls.
* Statistical significance found among the treatment groups according to Kruskal-Wallis One Way Analysis of Variance on ranks ($p < 0.05$) but unable to specify the groups that are significantly different from each other according to Dunnett's Method when the positive control groups (omeprazole, phenobarbital and rifampin) were included in the statistical analysis.
§ Statistical significance found among the treatment groups according to Kruskal-Wallis One Way Analysis of Variance on ranks ($p < 0.05$) but unable to specify the groups that are significantly different from each other according to Dunnett's Method when the positive control groups (omeprazole, phenobarbital and rifampin) were not included in the statistical analysis.
∞ Statistical significance found among the treatment groups according to One Way Analysis of Variance ($p < 0.05$) but unable to specify the groups that are significantly different from each other according to Dunnett's Method when the positive control groups (omeprazole, phenobarbital and rifampin) were not included in the statistical analysis.

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

In-vitro studies were conducted to determine whether pomalidomide is a substrate or an inhibitor of P-gp (study DMPK-037).

Using monolayers of MDCK cells (wild type (WT) or MDR1), the apparent permeability (Papp) was determined for pomalidomide (1 – 10 uM) in a bidirectional method (A→B and B→A), which was performed in the presence of P-gp inhibitors verapamil (250 uM) and ketoconazole (25 uM). Results show that pomalidomide was found to be a substrate of P-gp. The net efflux ratios (R_E MDR1/R_E WT) were 2.65, 4.72, and 5.36 at 1, 5, and 10 uM of pomalidomide. Also, the efflux ratio of 13.0 for pomalidomide (5 uM) in MDCK-MDR1 cells decreased to 1.72 and 1.37 in the presence of verapamil and ketoconazole, respectively.

In addition, the potential for pomalidomide to inhibit P-gp was measured by determining Papp for the P-gp substrate digoxin (100 nM) in the presence and absence of pomalidomide (0.03 – 10 uM) or positive control inhibitors (verapamil and ketoconazole). Pomalidomide had < 32% inhibition of digoxin in MDCK-MDR1 cells.

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

In-vitro studies (DMPK-043) were performed to assess the inhibition potential of pomalidomide (2 and 20 umol/L) for BCRP in the presence or absence of pomalidomide for 60 minutes. BCRP expressing porcine kidney epithelial LLC-PK1 cell and control LLC-PK1 cells were investigated in both the apical to basolateral (A→B) and the basolateral to apical (B→A) directions. Positive control included Ko143 inhibitor. Results show that following incubation of [^{3}H]-prazosin with pomalidomide at 2 uM and 20 uM, transporter activity was 88.1% and 85.9% of control, respectively (**Table 10**). Study results suggest that pomalidomide is not a strong inhibitor of BCRP.

In addition, *in-vitro* studies were performed to asses the inhibition potential of pomalidomide (2 and 20 umol/L) with the following transporters and corresponding substrates 1) OAT1: substrate [^{3}H]-p-aminohippuric acid (1 uM) for 2 minutes; 2) OAT3: substrate [^{3}H]-estrone sulfate (50 nmol/L) for 2 minutes;

3) OCT2: substrate [^{14}C]-metformin (10 uM) for 5 minutes in S2 cells expressing OCT2; 4) OATP1B1 & OATP1B3: substrate [^{3}H]-estradiol glucuronide (50 nM) for 2 minutes in HEK293 cells expressing transporter. Results show that at higher concentrations (20 umol/L), pomalidomide inhibited OAT1 by 26% and OAT3 by 30% (**Table 11**).

Table 10: Summary of Inhibitory Effects of CC-4047 (Pomalidomide) and Ko143 on [^{3}H]-Prazosin Transport across Control Cell and BCRP expressing Cell Monolayers

Substrate	Test article or Inhibitor		Control cells			BCRP expressing cells			R	% of control
			P_{app} ($\times 10^{-6}$ cm/sec)		P_{app} ratio	P_{app} ($\times 10^{-6}$ cm/sec)		P_{app} ratio		
		Concentration (µmol/L)	Apical to basal	Basal to apical		Apical to basal	Basal to apical			
[^{3}H]-Prazosin	CC-4047	0	42.7 (1.2)[a]	45.5 (1.2)	1.1	7.0 (0.2)	103.3 (1.4)	14.8	13.5	100.0
		2	45.9 (0.9)	50.1 (1.2)	1.1	8.4 (0.6)	109.7 (5.3)	13.1	11.9	88.1
		20	43.5 (1.8)	50.2 (4.4)	1.2	8.2 (0.7)	114.2 (2.0)	13.9	11.6	85.9
	Ko143	0.3	44.2 (2.7)	43.0 (0.8)	1.0	43.7 (1.0)	50.5 (1.5)	1.2	1.2	8.9
[^{14}C]-Mannitol	NA	NA	9.5 (2.6)	3.7 (1.5)	0.4	10.2 (3.0)	6.5 (2.5)	0.6	1.5	NA

[a] values are mean (and standard deviation) of three replicates; NA: not applicable

Table 11: Summary of Inhibitory Effects of CC-4047 (Pomalidomide) on OAT1, OAT3, OCT2, OATP1B1 and OATP1B3 Mediated Uptake

	OAT1-mediated uptake of [^{3}H]-PAH			OAT3-mediated uptake of [^{3}H]-E3S			OCT2-mediated uptake of [^{14}C]-metformin[a]			OATP1B1-mediated uptake of [^{3}H]-$E_2$17βG			OATP1B3-mediated uptake of [^{3}H]-$E_2$17βG		
CC-4047 (µmol/L)	Control cells	OAT1 expressing cells	% of control	Control cells	OAT3 expressing cells	% of control	Control cells	OCT2 expressing cells	% of control	Control cells	OATP1B1 expressing cells	% of Control	Control cells	OATP1B3 expressing cells	% of control
0	0.689 (0.149)[b]	43.9 (1.3)	100.0	2.29 (0.23)	24.0 (0.6)	100.0	1.11 (0.08)	11.3 (1.0)	100.0	0.505 (0.235)	8.01 (0.33)	100.0	0.515 (0.116)	8.32 (0.34)	100.0
2	0.609 (0.096)	42.7 (1.2)	97.4	2.50 (0.04)	28.3 (2.0)	118.8	1.09 (0.08)	11.3 (0.8)	100.2	0.345 (0.054)	8.07 (0.15)	102.9	0.877 (0.189)	8.11 (0.23)	92.7
20	0.584 (0.084)	32.6 (1.4)	74.1	2.65 (0.25)	17.8 (1.1)	69.8	1.08 (0.13)	16.7 (1.1)	153.3	0.276 (0.132)	8.46 (0.79)	109.0	1.07 (0.33)	7.97 (0.10)	88.4
Probenecid[c]	0.499 (0.130)	3.30 (0.12)	6.5	2.55 (0.27)	2.92 (0.10)	1.7	NA	NA	NA	NA	NA	NA	NA	NA	NA
Quinidine[d]	NA	NA	NA	NA	NA	NA	0.525 (0.035)	2.57 (0.12)	20.1	NA	NA	NA	NA	NA	NA
Rifampicin[e]	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.266 (0.020)	0.449 (0.027)	2.4	0.460 (0.156)	1.02 (0.43)	7.2

PAH: p-Aminohippuric acid (1 µmol/L); E3S: Estrone sulfate (50 nmol/L); $E_2$17βG: Estradiol glucuronide (50 nmol/L); NA: not applicable

[a] metformin at 1 µmol/L; [b]: values are mean (and standard deviation) of three replicates; [c]: probenecid at 100 µmol/L; [d]: quinidine at 300 µmol/L; [e]: rifampicin at 10 µmol/L.

2.4.2.6 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

The sponsor proposes to use pomalidomide in combination with [redacted] (b) (4) dexamethasone. The potential for drug-drug interaction between the two drugs was assessed in study MM-002 (**Table 12**). This was a randomized, open-label study in refractory or relapsed MM patients. Patients received 4 mg of pomalidomide plus 40 mg of dexamethasone or pomalidomide alone. Pharmacokinetic samples were collected on day 1 and day 8 in a sub-set of patients (n=14). The Cmax and AUC of pomalidomide were similar in the presence and absence of dexamethasone, indicating that dexamethasone does not influence the exposure to pomalidomide (**Table 12**).

Table 12: Summary of Mean Pomalidomide Plasma PK Parameters by Treatment and Study Day Following Oral Doses of Pomalidomide 4 mg alone and in Combination with Dexamethasone (Study MM-002)

		N		Geometric Mean (CV%)	
Treatment	**Parameter**	**Day 1**	**Day 8**	**Day 1**	**Day 8**
Pomalidomide (4 mg) + dexamethasone	AUC_{0-t}	7	7	300 (39.9)	381 (55.2)
	C_{max}	7	7	62.4 (28.1)	73.2 (35.3)
	T_{max}[a]	7	7	2.00 (1.00-3.00)	3.00 (2.00-6.00)
Pomalidomide (4 mg)	AUC_{0-t}	7	5	314 (43.9)	411 (28.2)
	C_{max}	7	5	64.6 (39.2)	78.8 (27.7)
	T_{max}	7	5	2.00 (1.00-4.00)	2.00 (1.00-3.00)

2.4.2.7 What other co-medications are likely to be administered to the target patient population?

Currently the proposed label recommends that patients take pomalidomide (b) (4)

2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

No other *in-vivo* drug-drug interaction studies with pomalidomide have been performed.

2.4.2.9 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

Clinical drug interaction studies with pomalidomide will need to be performed to address *in-vitro* metabolism findings.

2.5 General Biopharmaceutics

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

The applicant has classified pomalidomide as a BCS Class (b) (4) compound, based on the 4 mg dose. However, it has not received an official BCS classification/designation from the FDA.

Solubility

The solubility of pomalidomide was tested in different pH buffers and different solvents. Pomalidomide at the 2 mg strength was found to be soluble in 250 mL of aqueous media for pH values 1.2, 4.5 and 6.8, but 4 mg (clinical dose) was not soluble. The solubility of pomalidomide does not appear to be pH dependent. Listed in **Table 13** is the solubility of pomalidomide at 37° C at different pH levels.

Table 13: Solubility at Saturation in Aqueous Media as a Function of pH at 37° C

Theoretic pH (Buffered Solution)	**Solubility of Pomalidomide after 24 hours (ug/mL)**
1.2 (0.05N HCL)	15.0
4.5 (0.05M acetate)	14.6
6.8 (0.05M phosphate)	13.2

Permeability

The *in-vitro* permeability of pomalidomide was evaluated using MDCK cells (either wild type (WT) or MDR1). The apparent permeability (Papp) was evaluated for 1, 5 and 10 uM of pomalidomide in the presence of P-gp inhibitors verapamil (250 uM) and ketoconazole (25 uM). Results show moderate intrinsic permeability based on Papp values. Pomalidomide showed higher permeability with MDCK-MDR1 cells in the BA direction than in the AB direction. Net efflux ratios were 2.65, 4.72 and 5.36 at 1, 5 and 10 uM of pomalidomide, respectively.

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

With the exception of different dyes for each capsule shell, the to-be-marketed capsule formulation is identical to the formulation used in the pivotal Phase 2 clinical trials. The 1 mg and 2 mg capsule formulation were used in the registration trial (MM-002). The 3 mg and 4 mg capsule formulation used a (b) (4) as the 1 mg and 2 mg formulation. A bridging BE study (CP-007) was performed to evaluate the 3 mg and 4 mg capsules (test) with the 1 mg and 2 mg capsule formulation (reference). See details of study CP-007 in section 2.5.2.1.

2.5.2.1 What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80 – 125%?

The applicant performed two BE studies. The first BE study (CP-005) was performed to assess the equivalence of a new test formulation (2 mg) compared to the reference formulation (2 mg). Results show that C_{max} did not meet the FDA's 80 – 125% BE criteria, therefore the applicant will not use this test formulation for the commercial product.

The second BE study (CP-007) evaluated the 3 mg and 4 mg capsules formulation in healthy subjects. The objective was to evaluate the BE of a new 3 mg (test) capsule formulation vs. 1 mg plus 2 mg (reference) capsules and 4 mg (test) formulation vs. 2 mg plus 2 mg (reference) capsules. Results show that the 3 mg and 4 mg capsules test formulations was similar to the reference formulations. The 90% confidence intervals of the geometric least square mean between the two formulations (3 mg vs. 1 mg + 2 mg and 4 mg vs. 2 x 2 mg) were within the 80 – 125% BE criteria for AUC and C_{max}. **Table 14** and **Table 15** provide the PK findings for both the 3 mg and 4 mg capsule comparison, respectively.

Table 14: Statistical Comparison of the PK Parameters of Pomalidomide between Treatment A (3 mg test) and Treatment B (1 mg + 2 mg reference)

PK parameters	Geometric Mean		Ratio (%) of Geometric Means (C/D)	90% CI of Ratio (%) of Geometric Means	Intra subject CV%
	Treatment C (Test) N=35	Treatment D (Reference) N=35			
AUC_{0-t} (ng•hr/mL)	354.0	344.0	102.9	(99.9, 106.0)	7.3
AUC_{0-inf} (ng•hr/mL)	358.7	348.4	102.9	(100.0, 106.0)	7.1
C_{max} (ng/mL)	42.3	41.1	102.8	(98.7, 107.0)	9.9

AUC_{0-inf} = area under the plasma concentration-time curve from time zero extrapolated to infinity; AUC_{0-t} = AUC from time zero to the last measurable time point; C_{max} = maximum observed concentration; hr = hour; PK = pharmacokinetic
Treatment C: A single 3-mg test pomalidomide capsule administered under fasted conditions
Treatment D: A single 1-mg reference pomalidomide capsule plus a single 2-mg reference pomalidomide capsule administered under fasted conditions

Table 15: Statistical Comparison of the PK Parameters of Pomalidomide between Treatment A (4 mg test) and Treatment B (2 x 2 mg reference)

PK Parameters	Geometric Mean		Ratio (%) of Geometric Means (A/B)	90% CI of Ratio (%) of Geometric Means	Intra subject CV%
	Treatment A (Test) N=36	Treatment B (Reference) N=35			
AUC_{0-t} (ng•hr/mL)	476.0	454.9	104.6	(101.2, 108.2)	8.3
AUC_{0-inf} (ng•hr/mL)	481.4	460.2	104.6	(101.2, 108.2)	8.3
C_{max} (ng/mL)	57.8	55.7	103.8	(99.0, 108.8)	11.8

AUC_{0-inf} = area under the plasma concentration-time curve from time zero extrapolated to infinity; AUC_{0-t} = AUC from time zero to the last measurable time point; C_{max} = maximum observed concentration; hr = hour; PK = pharmacokinetic
Treatment A: A single 4-mg test pomalidomide capsule administered under fasted conditions
Treatment B: Two 2-mg reference pomalidomide capsules administered under fasted conditions

2.5.3 What is the composition of the to-be-marketed formulation?

The applicant proposes to market pomalidomide capsules in the strengths of 1, 2, 3 and 4 mg. The formulation used in the registration trials is the same as the to-be-marketed formulation. Listed in **Table 16** is the proposed formulation.

Table 16: Composition of Pomalidomide IR Capsules: 1 mg, 2 mg, 3 mg, and 4 mg

			1 mg Capsule	2 mg Capsule	3 mg Capsule	4 mg Capsule
Ingredient	Quality Standard	Function	Theoretical Weight per Capsule (mg)			
Pomalidomide (CC-4047)	In-house	Active ingredient	1.00	2.00	3.00	4.00
Mannitol	USP-NF/Ph. Eur.	(b) (4)	(b) (4)			
Starch, pregelatinized	NF/Ph. Eur.					
Sodium stearyl fumarate	NF/Ph. Eur.					
						(b) (4)

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2.5.4 What moieties should be assessed in bioequivalence studies?

Pomalidomide, the active ingredient of drug product, should be assessed in human plasma for BE studies.

2.5.5 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Study CP-005 was a BE study to compare a new 2 mg test formulation to the 2 mg reference formulation. As a secondary objective, the effect of a high fat, high calorie meal on the pharmacokinetics of pomalidomide 2 mg test formulation (**Table 17**) was evaluated. Results showed that the 2 mg test formulation failed to meet the BE criteria to the reference formulation. Because the food effect evaluation was conducted using the test formulation that was not bioequivalent to the reference product or to the commercial formulation, food effect results of study CP-005 were deemed inappropriate to determine the influence of food on the exposure to pomalidomide. In addition, food effect studies were not conducted with the final market formulation. Furthermore, all clinical pharmacology studies were performed under a fasted state. Patients in the pivotal efficacy study, MM-002, were instructed to take drug 2 hours before and 2 hours after eating. The applicant will need conduct a food effect study using the commercial formulation of pomalidomide.

Until the influence of food is evaluated in a properly designed study, the label will provide instruction to take the pomalidomide under fasting condition. In all clinical and clinical pharmacology studies, pomalidomide was administered under fasting conditions.

Table 17: Plasma PK Parameters for Pomalidomide in Two Different Formulations, and in Fed and Fasted Conditions, in Healthy Male Subjects (Study CP-005)

	Pomalidomide Dose Level (2 mg)		
PK Parameter	Reference Fasted (N=27)	Test Fasted (N=28)	Test Fed (N=26)
AUC_{0-t} (ng•hr/mL)	(b) (4)		
AUC_{0-inf} (ng•hr/mL)			
C_{max} (ng/mL)			
T_{max}[a] (hr)			
$t_{1/2}$ (hr)			
CL/F (L/hr)			
Vz/F (L)			

AUC_{0-inf} = area under the plasma concentration-time curve from time zero extrapolated to infinity; AUC_{0-t} = AUC from time zero to time *t*, where *t* is the last measurable time point; CL/F = apparent total plasma clearance; C_{max} = maximum observed concentration; hr = hour; PK = pharmacokinetic; $t_{1/2}$ = terminal elimination half-life; T_{max} = time to C_{max}; Vz/F = apparent total volume of distribution

[a] Median (minimum, maximum) presented for T_{max}

2.5.6 How do the dissolution conditions and specification ensure in vivo performance and quality of the product?

The following method was proposed for dissolution purposes for pomalidomide:

Apparatus:	USP Apparatus 2 (Paddle Method)
Rotation Speed:	50 rpm
Medium:	0.1 N HCL
Volume:	900 mL
Acceptance Criteria:	Q= (b) (4) at 45 minutes

2.6 Analytical Section

2.6.1 Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

Pomalidomide was evaluated in human plasma, urine and semen using a validated LC/MS/MS method. Metabolites were analyzed in plasma, urine and feces in the mass balance study (CP-004) with a non-validated HPLC method. Metabolites were found to be present < 10% relative to parent and relative to total radioactivity.

2.6.2 Which metabolites have been selected for analysis?

Metabolites were only analyzed in the mass balance study following 2 mg of [^{14}C]-pomalidomide in healthy subjects. No metabolites were analyzed further in clinical studies, other than the mass balance study.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Total pomalidomide concentrations were measured. Pomalidomide (30 – 1000 ng/mL) enantiomers expressed low to moderate protein binding in human plasma. Protein binding for the R-Enantiomer (CC-6016) in human plasma ranged from 11.96 to 24.85% and S-Enantiomer (CC-5083) ranged from 40.11 to 43.94%.

2.6.4 What bioanalytical methods are used to assess concentrations?

LC/MS/MS was used to measure the concentrations of pomalidomide in plasma, urine and semen. Listed in **Table 18** is a summary of analytical methods.

Table 18: Summary of Bioanalytical methods for Pomalidomide from Clinical Studies

Studies	Matrix/ Analytes	Method	Assay Performance description
1398/130-D0142	Plasma/ pomalidomide	LC-MS/MS	Lower limit of quantification: 0.2 ng/mL Calibrated Range: 0.2 to 50 ng/mL , Intra-assay Precision (%CV): ≤7.5% Inter-assay Precision (%CV): ≤ 9.3% Intra-assay Accuracy (% Diff): 5.3-13.3% Inter-assay Accuracy (%Diff): 8.0-13.3% Freeze/Thaw Stability: 3 cycles @ -20 C Bench Top Stability: 3 hours at RT Long-term Stability: 34 days at - 70 C Extract Stability: At least 24 hours at - 20 C
1398/176-D0142	Urine/ pomalidomide	LC-MS/MS	Lower limit of quantification: 20 ng/mL Calibrated Range: 20 to 4000 ng/mL , Intra-assay Precision (%CV): <6.7% (at LLOQ) & ≤ 12.6 % (at all other QC levels) Inter-assay Precision (%CV): < 15.7% Intra-assay Accuracy (% Diff): -7.1 to 5.6% Inter-assay Accuracy (%Diff): -8.2 to 2.2% Freeze/Thaw Stability: 3 cycles @ -20 C Bench Top Stability: 3 hours at RT Long-term Stability: 55 days at - 70 C Extract Stability: at least 24 hours at - 20 C
DMPK-033 (amendment 2)	Plasma/ pomalidomide	LC-MS/MS	Lower limit of quantification: 0.5 ng/mL Calibrated Range: 0.5 to 200 ng/mL Intra- and Inter-day Precision (%CV): ≤ 10.15% and ≤ 8.40%, respectively Intra-assay Accuracy (% RE): -2.36 – 0.60% Freeze/Thaw Stability: 3 cycles @ -70 C Bench Top Stability: 20 hours at RT Long-term Stability: 785 days at - 70 C and 369 days at - 20 C Reinjection Reproducibility: 82 hours, RT; 170 hours at 4 C
DMPK-36 (amendment 1)	Plasma/ pomalidomide	LC-MS/MS	Lower limit of quantification: 0.25 ng/mL Calibrated Range: 0.25 to 100 ng/mL , Inter- & Intra-assay Precision (%CV): 6.06 to 8.54% Inter- & Intra-assay Accuracy (%RE): -3.8 to -0.45% Freeze/Thaw Stability: 5 cycles @ -70 C Bench Top Stability: 6 hours at RT Long-term Stability: up to 477 days at - 20 C and up to 482 days at - 70 C Reinjection Reproducibility: 89 hours at RT
DMPK-1217 Report not provided. Results from applicant's summary.	Semen/ pomalidomide	LC-MS/MS	Lower limit of quantification: 0.5 ng/mL Calibrated Range: 0.5 to 100 ng/mL Inter-assay Precision (%CV): < 4.26% Intra-assay Precision (%CV): < 4.53% Inter-assay Accuracy (%Diff): 4.47 – 9.67% Intra-assay Accuracy (% Diff): 2.68 – 13.20% Long-term Stability: 36 days at - 20 C and - 70 C

2.6.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies?

See section 2.6.4 above.

2.6.6 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

See section 2.6.4 above.

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/s/

RACHELLE M LUBIN
12/20/2012

BAHRU A HABTEMARIAM
12/21/2012

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	204026/N-000
Submission Date:	Original: 04/10/12, Amendments: 05/11/12, 10/29/12, 12/03/12, and 12/12/12
Brand Name:	TBD
Generic Name:	Pomalidomide
Formulation:	Immediate release (IR) capsules
Strength:	1, 2, 3, and 4 mg (4 strengths)
Applicant:	Celgene
Type of submission:	Original (standard 10-month review)
Reviewer:	Tien-Mien Chen, Ph.D.

SYNOPSIS

Background

Pomalidomide is an NME (new molecular entity), which was developed by Celgene under IND 66,188. In combination with dexamethasone, pomalidomide is indicated for patients with relapsed and refractory multiple myeloma (MM) 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.

Pomalidomide is an analog of thalidomide, an agent which is a known human teratogen that can cause severe life-threatening birth defects. Pomalidomide has demonstrated teratogenic activity in both rats and rabbits when administered during the period of major organogenesis.

The 1 and 2 mg capsule formulations (b) (4) have been tested in major clinical studies. They are the same as the TBM (to-be-marketed) formulations except for the differences in capsule shell dye components. The two higher capsule strengths, 3 and 4 mg, (b) (4) the same as the TBM formulations, and employed in the BE (bioequivalence) study only. (b) (4) The BE study (No. **CC-4047-CP-007**) provides the link for the 1 and 2 mg capsule strengths vs. the 3 and 4 mg capsule strengths.

Current Submission

On 04/10/12, Celgene submitted the original NDA 204026 for pomalidomide IR capsules, 1, 2, 3, and 4 mg. The NDA included CMC information, comparative dissolution profile data/information, and a BE study No. **CC-4047-CP-007**.

Upon request, the Applicant submitted:

- On 12/03/12, a biowaiver request with supporting dissolution data in order to bridge the two proposed manufacturing sites for the TBM drug products, i.e., Celgene International Sarl site and the (b) (4) site. The TBM drug products manufactured at Celgene International Sarl site have never been tested clinically.
- On 12/12/12, additional analyses on the relationship of (b) (4) for the drug substance (DS) lots made for clinical supplies and drug product (DP) batches made at both proposed manufacturing sites.

Biopharmaceutics Review

The Biopharmaceutics review is focused on the evaluation and acceptability of (1) the proposed dissolution method and acceptance criterion, (2) the comparative dissolution profile data supporting the biowaiver request, and (3) the relationship between (b) (4)

RECOMMENDATION

ONDQA-Biopharmaceutics has evaluated the information included in NDA 204026 and has the following comments:

1. The following dissolution method and the acceptance criterion are acceptable.

Product Name	**USP Apparatus**	**Rotation Speed (rpm)**	**Dissolution Volume Medium/Temperature**	**Acceptance Criterion** (% Label Claim Dissolved)
Pomalidomide IR Capsules	USP II (Paddle)	50 rpm	**900 ml** of 0.1 N HCl at 37°C	Q = (b) (4) at 45 minutes

2. The Applicant's request for a waiver of the BE study between the two proposed drug product manufacturers sites for the TBM drug products at Celgene International Sarl site and at (b) (4) site is acceptable.

3. The results from the additional analyses submitted on 12/12/12 showed that there is no relationship between (b) (4) for the DS lots manufactured for clinical use or the DP batches made from both manufacturing sites.

From the ONDQA-Biopharmaceutics perspective, NDA 204-026 for Pomalidomide IR Capsules is recommended for approval.

Tien-Mien Chen, Ph.D.
ONDQA Biopharmaceutics Reviewer

12/10/12
Date

Angelica Dorantes, Ph.D.
ONDQA Biopharmaceutics Team Leader

12/12/12
Date

CC: DARRTS/NDA 204026/RLostritto

PRODUCT QUALITY - BIOPHARMACEUTICS ASSESSMENT

BACKGROUND

Pomalidomide is an NME (new molecular entity) which was developed by Celgene under IND 66,188. Pomalidomide belongs to the class of immunomodulatory drugs known as IMiDs. In combination with dexamethasone, pomalidomide is indicated for patients with relapsed and refractory MM 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.

The proposed dosing regimen is 4 mg orally QD on Days 1-21 of repeated 28-day cycles until disease progression. (b) (4)

Pomalidomide is an analog of thalidomide, an agent which is a known human teratogen that can cause severe life-threatening birth defects. Pomalidomide has demonstrated teratogenic activity in both rats and rabbits when administered during the period of major organogenesis.

Pomalidomide is reported as a chiral molecule, but is manufactured as a racemic mixture of S- and R-enantiomers (b) (4) The enantiomers interconvert *in vitro* in buffer at neutral pH and in plasma. The interconversion appears to occur via both enzymatic and non-enzymatic pathways since gradual racemization (approximate half-life of 24 hrs) was observed *in vitro* in buffer (pH 7) and more rapid racemization (1:1 ratio achieved by approximately 4 hours) was observed in monkey and human plasma *in vitro*. Pomalidomide capsules are provided in high density polyethylene (HDPE) bottles with tamper evident (induction sealed), child resistant (b) (4) caps.

CURRENT SUBMISSION

On 04/10/12, Celgene submitted the original NDA 204026/N-000 for pomalidomide IR capsules, 1, 2, 3, and 4 mg. Included in the NDA were CMC information, comparative dissolution profile data/information and a BE (bioequivalence) study No. **CC-4047-CP-007**.

Further Communications with the Applicant:

Upon request, on 12/03/12, the Applicant submitted a biowaiver request with supporting dissolution data in order to bridge the two proposed manufacturing sites for the TBM drug products, i.e., Celgene International Sarl site and the (b) (4) site.

On 12/10/12, a teleconference (TCON) was held between the Applicant and FDA for clarification and discussions on additional analyses. During the meeting the Applicant agreed to implement the recommended dissolution criterion of Q = (b) (4)% at 45 minutes.

On 12/12/12, the Applicant submitted the data from the additional analyses. The results showed no correlations between (b) (4)

(b) (4) for the DP lots manufactured for clinical use or the DP batches made from both manufacturing sites. Also, the Applicant submitted the updated specification table for the drug product with the revised dissolution acceptance criterion.

BIOPHARMACEUTICS REVIEW

The Biopharmaceutics review is focused on the evaluation and acceptability of (1) the proposed dissolution method and acceptance criterion, (2) the comparative dissolution profile data supporting the biowaiver request, and (3) the relationship between (b) (4)

FORMULATION COMPARISONS

The proposed composition/formulations for the 4 capsule strengths are shown below.

Table 1. Qualitative and Quantitative Composition of Pomalidomide IR Capsules, 1 mg, 2 mg, 3 mg, and 4 mg

			1 mg Capsule	2 mg Capsule	3 mg Capsule	4 mg Capsule
Ingredient	**Quality Standard**	**Function**	**Theoretical Weight per Capsule (mg)**			
Pomalidomide (CC-4047)	In-house	Active ingredient	1.00	2.00	3.00	4.00
Mannitol	USP-NF/Ph. Eur.	(b) (4)				(b) (4)
Starch, pregelatinized	NF/Ph. Eur.					
Sodium stearyl fumarate	NF/Ph. Eur.					
Total Capsule Fill Weight						(b) (4)

The 1 and 2 mg capsule formulations are (b) (4) and have been tested in major clinical studies. They are the same as the TBM formulations except for the differences in capsule shell dye components. The two higher capsule strengths, 3 and 4 mg, are: (1) (b) (4) (2) The same as the TBM formulations, and (3) Employed in the BE study only. (b) (4) (Table 1).

The BE study (No. **CC-4047-CP-007**) provides the link between the clinically tested formulation of 1 and 2 mg capsule strengths and the 3 and 4 mg capsules strengths in a two-way crossover, single-dose PK study in healthy subjects, i.e., **Part 1**: 3 mg vs. (1+2) mg and **Part II**: 4 mg vs. (2+2) mg. The BE study will be reviewed by OCP.

There are two proposed drug product manufacturers, (b) (4) and Celgene International Sarl sites. The drug product batches that have been tested clinically were manufactured by (b) (4) site, but NOT the Celgene International Sarl site. Upon the FDA's request on 11/21/12, a biowaiver was submitted on 12/03/12 with supporting comparative dissolution profile data to link the Celgene International Sarl site to the (b) (4) site.

DISSOLUTION METHODOLOGY AND ACCEPTANCE CRITERION
The proposed dissolution method and acceptance criterion are shown below.

USP Apparatus:	**II (Paddle)**
Rotational Speed:	**50 rpm**
Medium:	**0.1 N HCl, 900 mL at 37°C**
Acceptance Criterion :	**Q= (b) (4) % at 45 min**

The Applicant however did not explore fully on the dissolution methodology nor provide justification for the selection of the above dissolution method. Therefore, a Biopharmaceutics information request was sent to the Applicant on 09/12/12 asking for the needed dissolution information. The Applicant responded on 10/29/12. The provided information is summarized below.

A. <u>Dissolution Development Report</u>:

I. pH Buffers:

Table 2. Solubility of Pomalidomide Drug Substance in Bio-Relevant pH buffers

Solution pH	Solubility (µg/mL) at 24 hours
	(b) (4)

Table 3. Summary of Pomalidomide Mean Dissolution Profile in Bio-Relevant pH Buffers (n=12/Lot)

Dissolution medium	Lot #	10 min	20 min	30 min	45 min	60 min	90 min
	1mg						
(b) (4)							

Figure 1: Dissolution Profiles of 1 mg Pomalidomide Capsules at Different pH

Figure 2: Dissolution Profiles of 4 mg Pomalidomide Capsules at Different pH

II. Apparatus and Rotational Speed:

Table 4. Dissolution Profile Results of Pomalidomide Capsules Using USP (b) (4) Apparatus II

Dissolution Instrument	Lot #	10 min	20 min	30 min	45 min	60 min	90 min
	1mg						
	(b) (4)						
Apparatus II 50RPM	(b) (4)						
	4mg						
	(b) (4)						
Apparatus II 50RPM	(b) (4)						

Figure 3. Dissolution Profiles of 1 mg Pomalidomide Capsules Using USP (b) (4) Apparatus II

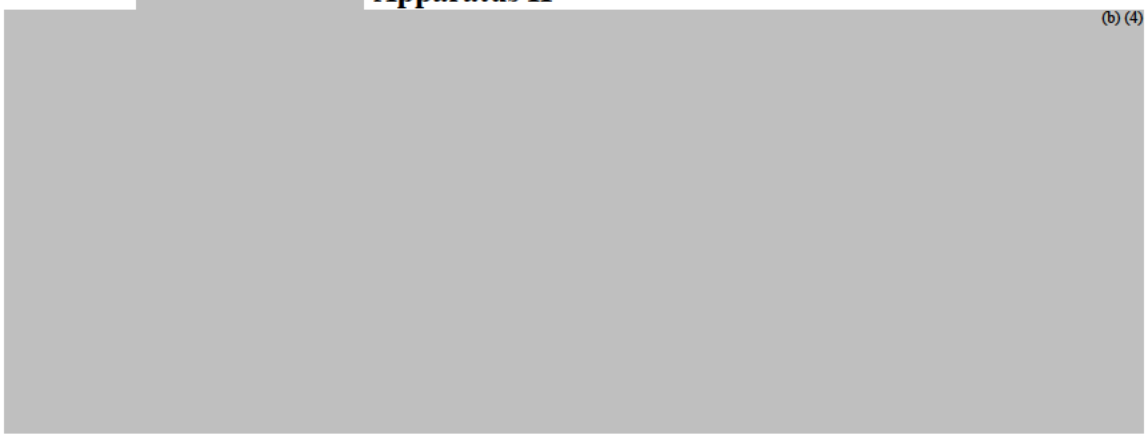
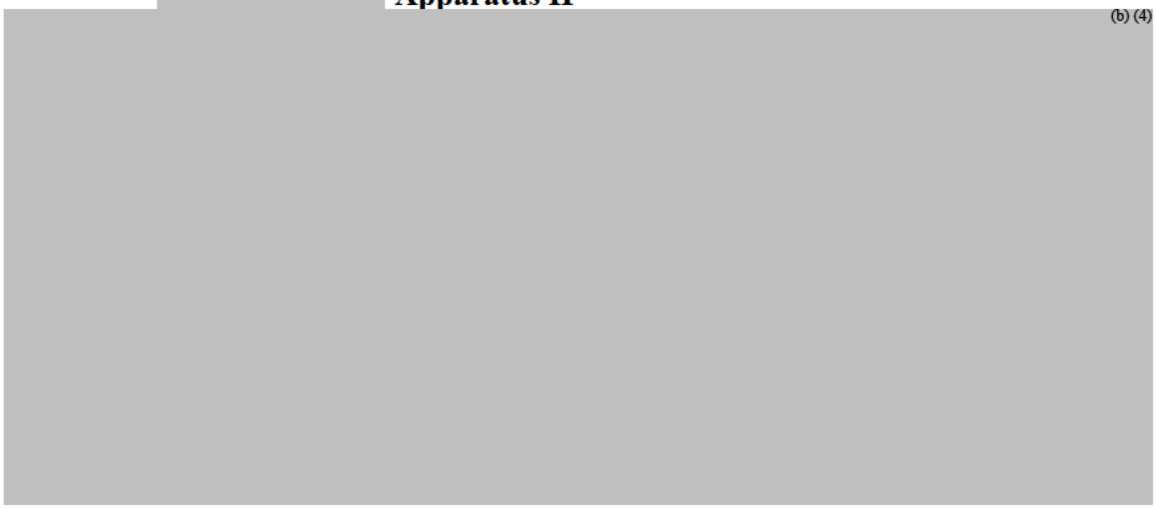


Figure 4. Dissolution Profiles of 4 mg Pomalidomide Capsules Using USP (b) (4) Apparatus II



The Applicant concluded that the mean dissolution profiles are similar using these methods and the USP II (paddle) was selected.

III. USP Paddle with Different RPMs:

Table 5. Mean Dissolution Profile Results of Pomalidomide Capsules Using USP Apparatus II with Different Paddle Speeds

Paddle Speed	Lot #	10 min	20 min	30 min	45 min	60 min	90 min
(b) (4)							

Figure 5. Mean Dissolution Profile of 1 mg Pomalidomide Capsules Using USP Apparatus II with Different Paddle Speeds

(b) (4)

Figure 6. Mean Dissolution Profile of 4 mg Pomalidomide Capsules Using USP Apparatus II with Different Paddle Speeds

(b) (4)

Based on the above data, the USP Apparatus II and a paddle speed of 50 rpm were selected

IV. Discriminating Power:

Table 6. Particle Size Data of Pomalidomide Drug Substance Batches

	Percentage of API	
Drug Substance Lot	Particle Size (b) (4)	Particle Size (b) (4)
F10-04602	(b) (4)	
F11-01608		
F11-01609		

Figure 7. Mean Dissolution Profiles of 1 mg Pomalidomide Capsules Using Different Particle Size Drug Substance Batches

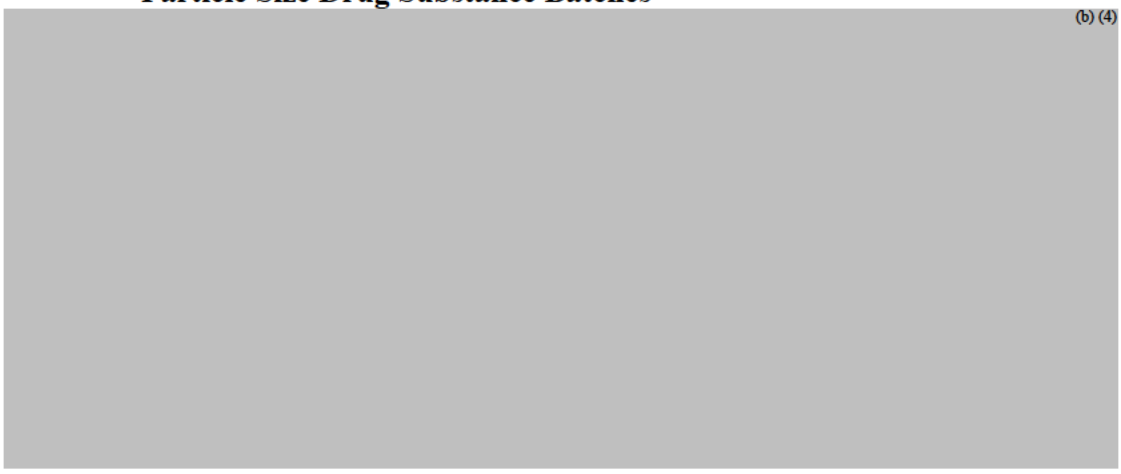


Figure 8. Mean Dissolution Profiles of Pomalidomide 1 and 3 mg Capsules Manufactured with Process B (Proposed for Commercial Process) vs. Process C for Drug Substance Batches (b) (4)

Based on the above results, Process B was selected for commercial use.

Note: [redacted]

Reviewer's Overall Evaluation: Acceptable
The provided dissolution development data support the Applicant's selection of the proposed dissolution method.

B. Proposed Dissolution Method and Acceptance Criteria
Based on the above dissolution development/exploration studies, the Applicant proposed the following dissolution method and acceptance criterion.

Method: USP II (Paddle) with 50 rpm in 900 ml of 0.1 N HCl Medium
Acceptance Criterion: Q=[redacted]% at 45 min

The Applicant also submitted the complete dissolution profile data (n=12/lot) for the registration stability (commercial, TBM) formulation batches, 1, 2, 3, and 4 mg tested as shown below in Figure 9 using the proposed dissolution method.

Figure 9. Mean Dissolution Release Profile for Pomalidomide IR Capsules Registration Stability Batches (n=12/Lot; [redacted]

[redacted]

Note : Primary stability batch Nos. 10D0036 (1 mg), 10D0040 (2 mg), 10D0042 (3 mg), and 10D0045 (4 mg) tested.

Reviewer's Evaluation:
The proposed dissolution method is acceptable. However, the proposed acceptance criterion of Q = [redacted] is not supported by the data and is not acceptable. Therefore, on 12/07/12 FDA sent an information request including the following Biopharmaceutics comments:

1. The proposed dissolution acceptance criterion of [redacted] is not supported by the provided dissolution data. Therefore, the dissolution acceptance criterion [redacted] Q= [redacted]% at 45 min. Nevertheless, it must be recognized that

some batches may require Stage 2 and, occasionally, Stage 3 testing. Please provide the updated specification table for the drug product with the revised dissolution criterion.

2. We have concerns that the observed variations in % dissolution of pomalidomide among the batches could be due to the (b) (4) Please analyze the (b) (4) and provide the information.

During a teleconference held on 12/10/12, the above comments were discussed and the Applicant agreed to provide the data requested in above comment No. 2 and to implement Q = (b) (4)% at 45 minutes as the dissolution acceptance criterion for their pomalidomide IR capsule product.

On 12/12/12, the Applicant provided the updated specification table for the drug product with the revised dissolution acceptance criterion. Also, the data for the additional analyses evaluating the (b) (4) Please see the results from the Applicant's additional analyses and this reviewer's comments in Section D, pages 18-21 of this review.

C. Biowaiver:

On 11/21/12, a Biopharmaceutics information request was sent to the Applicant, asking them to submit a BE waiver request for the bridging of the (b) (4) site and the Celgene International Sarl site. On 12/03/12, the Applicant responded and their responses are summarized below. The supportive mean comparative dissolution profile data between the (b) (4) site and Celgene International Sarl site were also submitted and are presented in the next Figures 10-13 and Tables 7-10.

Figure 10. Dissolution Profiles for Pomalidomide Capsules, 1 mg – (b) (4) (red) and Celgene International (blue)

Note: Batch Nos. 07B0019, 07B0044, 07B0067, 08B0062, 09B0046, 09B0076, and 11B0238 were clinical biobatches tested. Please see Module 3 Section 23P5 Control of Drug Product for details.

Table 7. Dissolution Profile Data for 1 mg Pomalidomide Capsules (Celgene International Technical Batches and (b) (4) Validation Batch)

Manufacturer (Lot Number)	Celgene International (T0038)	Celgene International (T0046)	Celgene International (T0047)	(b) (4) (004492)
Time, min	Mean % Dissolved (% RSD)			
10*	(b) (4)			
20*				
30*				
45*				
60				

Figure 11. Dissolution Profiles for Pomalidomide Capsules, 2 mg – (b) (4) (red) and Celgene International (blue)

(b) (4)

Note: Batch Nos. 06B0055, 07B0022, 07B0045, 07B0068, 08B0063, 09B0047, 09B0078, 09B0081, 09B0082, 09B0108, 09b0110, and 11B0239 were clinical biobatches.

Table 8. Dissolution Profile Data for 2 mg Pomalidomide Capsules (Celgene International Technical Batches and (b) (4) Validation Batch)

Manufacturer (Lot Number)	Celgene International (T0039)	Celgene International (T0040)	(b) (4) (004570)
Time, min	Mean % Dissolved (% RSD)		
10*	(b) (4)		
20*			
30*			
45*			
60			

Figure 12. Dissolution Profiles for Pomalidomide Capsules, 3 mg – (b) (4) (red) and Celgene International (blue)

Note: Batch Nos. 11B0135 was used in the BE study No. **CC-4047-CP-007**.

Table 9. Dissolution Profile Data for 3 mg Pomalidomide Capsules (Celgene International Technical Batches and (b) (4) Validation Batch)

Manufacturer (Lot Number)	Celgene International (T0041)	(b) (4) (10D0042)
Time, min		(b) (4)
10*		
20*		
30*		
45*		
60		

Figure 13. Dissolution Profiles for Pomalidomide Capsules, 4 mg – (b) (4) (red) and Celgene International (blue)

Note: It was not stated if the batch Nos. 11B0139 was used in the BE study No. **CC-4047-CP-007**.

Table 10. Dissolution Profile Data for 4 mg Pomalidomide Capsules (Celgene International Technical Batches and (b) (4) Validation Batch)

Manufacturer (Lot Number)	Celgene International (T0042)	(b) (4) (10D0045)
Time, min	Mean % Dissolved (% RSD)	
10*	(b) (4)	
20*		
30*		
45*		
60		

The Applicant concluded that there are (b) (4) Please see the Applicant's response dated 12/03/12.

This reviewer felt that the Applicant did not provide the complete dissolution data from the 3 primary stability batches for each strength and only presented one "selected" batch per each strength. Therefore, for quality control purposes and for setting an appropriate dissolution acceptance criterion, based on the available primary stability batches per each manufacturing site; Module 3 Section 32P5 Control of Drug Product, additional analyses were conducted by this reviewer as shown below in Figures 14-17 and Tables 11-14.

Figure 14. Dissolution Profile Data for 1 mg Pomalidomide Capsules (Celgene International Technical Batches and (b) (4) Primary Stability Batches)

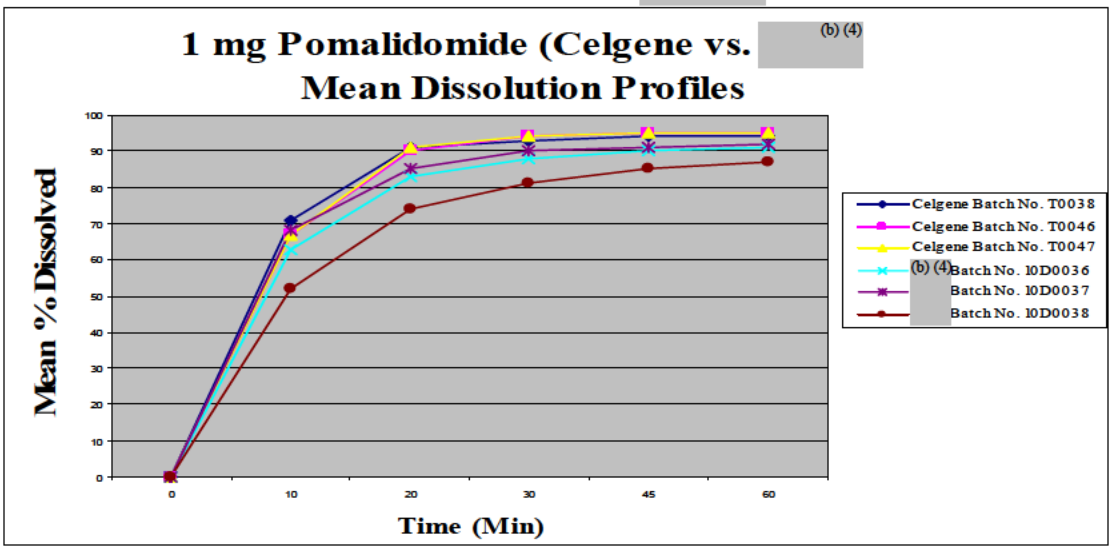


Table 11. Dissolution Profile Data for 1 mg Pomalidomide Capsules (Celgene International Technical Batches and (b) (4) UK Primary Stability Batches)

1 mg IR Capsules	Mean % Dissolved					
	Celgene				(b) (4)	
Time (Min)	T0038	T0046	T0047	10D0036	10D0037	10D0038
	(b) (4)					

Figure 15. Dissolution Profile Data for 2 mg Pomalidomide Capsules (Celgene International Technical Batches and (b) (4) Primary Stability Batches)

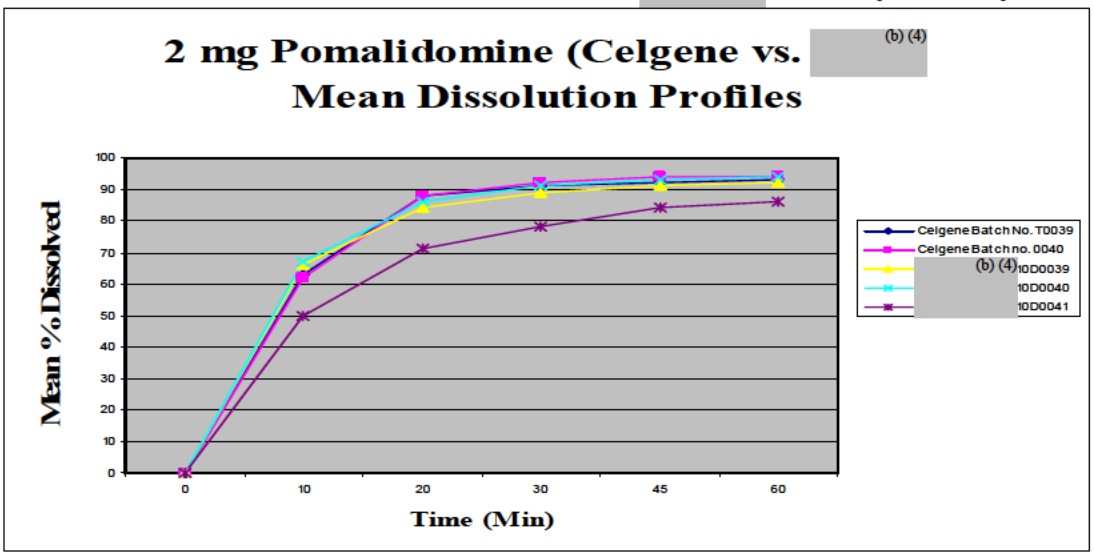


Table 12. Dissolution Profile Data for 2 mg Pomalidomide Capsules (Celgene International Technical Batches and (b) (4) Primary Stability Batches)

2 mg IR Capsules	Mean % D1ssolved				
	Celgene			(b) (4)	
Time (Min)	T0039	T0040	10D0039	10D0040	10D0041
	(b) (4)				

Figure 16. Dissolution Profile Data for 3 mg Pomalidomide Capsules (Celgene International Technical Batches and (b) (4) Primary Stability Batches)

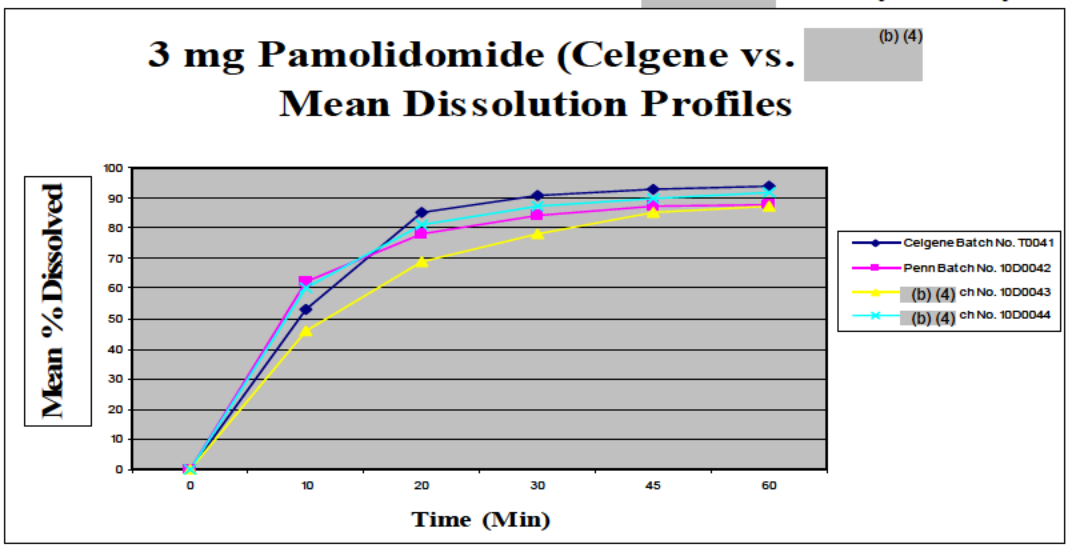


Table 13. Dissolution Profile Data for 3 mg Pomalidomide Capsules (Celgene International Technical Batches and (b) (4) Primary Stability Batches)

3 mg IR Capsules	Mean % Dissolved			
	Celgene		(b) (4)	
Time (Min)	T0041	10D0042	10D0043	10D0044
				(b) (4)

Figure 17. Dissolution Profile Data for 4 mg Pomalidomide Capsules (Celgene International Technical Batches and (b) (4) Primary Stability Batches)

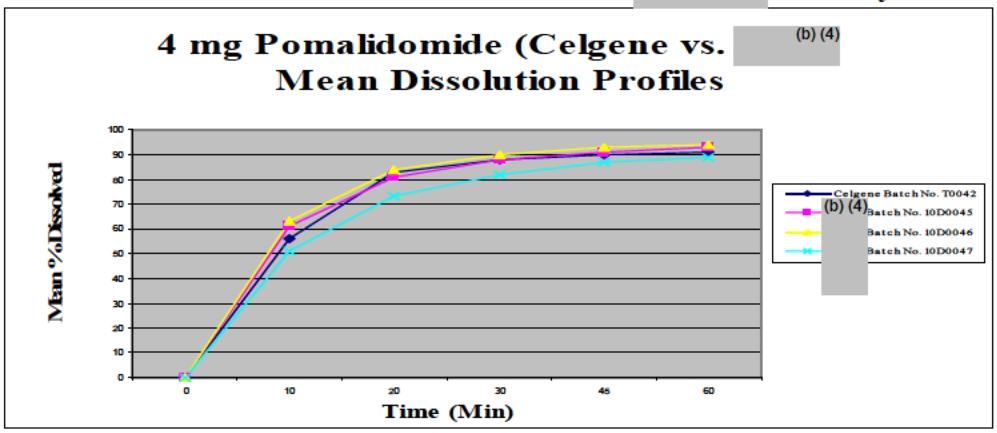


Table 14. Dissolution Profile Data for 4 mg Pomalidomide Capsules (Celgene International Technical Batches and Penn UK Primary Stability Batches)

4 mg IR Capsules	Mean % Dissolved			
	Celgene		Penn	
Time (Min)	T0042	10D0045	10D0046	10D0047
[redacted] (b) (4)				

D: Additional Analyses on the Correlations of [redacted] (b) (4)

Reviewer Comment

Since this Reviewer had concerns that the observed variations in [redacted] (b) (4) On 12/12/12, the Applicant provided the requested data. The results of the additional analyses are summarized below (Figures 18-19 for Clinical Supplies and Figures 20-23 for both proposed manufacturing sites for commercial products).

I. Clinical Supplies:

[redacted] (b) (4)

2 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

The reported [redacted] clinical supplies and in both proposed manufacturing sites for commercial drug products in Appendix 3 for details.

Reviewer's Comments:

1. The results from the additional analyses showed [redacted]

2. The root cause for showing [redacted] Q= [redacted]% a [redacted]

3. Nevertheless, the results of the additional analyses further support the FDA's recommended dissolution acceptance criterion of Q[redacted]% at 45 min, which was agreed upon in the 12/10/12 teleconference.

4. On 12/12/12, the Applicant also submitted the updated specifications table for the drug product with the revised dissolution acceptance criterion of Q=[redacted] at 45 min.

Reviewer's Overall Conclusions:

1. The following dissolution method and the acceptance criterion are acceptable.

USP Apparatus:	**II (Paddle)**
Rotational Speed:	**50 rpm**
Medium:	**0.1 N HCl, 900 mL at 37°C**
Acceptance Criterion :	**Q[redacted]% at 45 min**

2. The Applicant's request for a waiver of the BE study between the two proposed drug product manufacturers sites for the TBM drug products at Celgene International Sarl site and at [redacted] site is acceptable.

3. The results from the additional analyses submitted on 12/12/12 indicate that there is [redacted]

4. This NDA is considered acceptable from the Biopharmaceutics perspective.

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

/s/

TIEN MIEN CHEN
12/13/2012

ANGELICA DORANTES
12/14/2012

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

This is an original NDA for [redacted] (b) (4) (brand name pending, generic: pomalidomide), which is proposed for the treatment of multiple myeloma (MM). The proposed dosing regimen is 4 mg QD orally on Days 1-21 of repeated 28-day cycles (21/28 days) until disease progression; in combination with oral dexamethasone [redacted] (b) (4) The drug is formulated as a tablet with 1 mg, 2 mg, 3 mg, and 4 mg strengths. The NDA is based on 4 clinical studies in 552 subjects, in which pomalidomide was evaluated as a single agent or in combination with low dose dexamethasone. Two pivotal studies, studies CC-4047-MM-002 (conducted by Celegene) and IFM-2009-02 (investigator initiated), are used to support the proposed NDA. In addition, two supportive trials, studies CC-4047-MM-001 (conducted by Celegene) and PO-MM-PI-0010 (investigator initiated), provide supportive safety and efficacy data. Progression free survival was the primary endpoint for Study CC-4047-MM-002, while patient response rate was the primary endpoint for study IFM-2009-02. Secondary endpoints included duration of response, time to response, and overall survival.

To investigate the pharmacokinetic properties of pomalidomide, seven clinical studies have been conducted; five phase 1 studies in healthy subjects, and two phase 1b/2 studies in MM patients.

NDA/BLA Number:	20-4026	**SDN:**	000
Sponsor:	Celegene	**Date of Submission**	10-April-2012
Brand Name:	----------	**Generic Name:**	Pomalidomide
Drug Class:	Immunomodulatory Agent		
Dosage Form:	1, 2, 3 and 4 mg capsules		
Dosing Regimen:	4 mg QD on Days 1-21 of repeated 28-Day cycles (21/28)		
Route of Administration:	Oral		
Indication:	Multiple Myeloma		
OCP Division:	DCP5	**OND Division:**	DHP
OCP Reviewer:			
OCP Team Leader:	Bahru Habtemariam, Pharm. D. (acting Team Leader)		
PM Reviewer:			
PM Team Leader:			
GG Reviewer:			
GG Team Leader:			
Priority Classification:	☒ Standard ☐ Priority	**PDUFA Due Date**	10-Feb-2013
OCP Review Due Date:	----------	**OND Division Due Date:**	---------

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Critical Comments
Table of Contents present and sufficient to locate reports, tables, data, etc.	☒		
Tabular Listing of All Human Studies	☒		
Human PK Summary	☒		
Labeling	☒		
Bioanalytical and Analytical Methods	☒	5	1398/130-D0142, 1398/176-D0142, CC-4047-DMPK-033, CC-4047-DMPK-036, CC-4047-DMPK-1217
I. Clinical Pharmacology			
Mass balance:	☒	1	CC-4047-CP-004 (2 mg suspension) , CC-4047-CP-004-MB
Isozyme characterization:	☐		

Blood/plasma ratio:	☐		
Plasma protein binding:	☒	1	CC-4047-DMPK-015 (30, 100, 300, 1000 ng/mL)
Pharmacokinetics (e.g., Phase I) -	☐		
Healthy Volunteers:			
single dose:	☒	2	CC-4047-1398/132 (1, 5 mg capsule), CC-4047-CP-004 (2 mg suspension)
multiple dose:	☒	1	CC-4047-CP-006 (0.5, 1, 2 mg capsule)
Patients:			
single dose:	☐		
multiple dose:	☒	3	CDC-407-00-001/CC-4047-MM-001 (1, 5 mg capsule), CC-4047-MM-002 (0.5, 1, 2, 5 mg capsule)
Dose proportionality -			
fasting / non-fasting single dose:	☒	1	CC-4047-1398/132 (1, 5 mg capsule),
fasting / non-fasting multiple dose:	☒	1	CC-4047-CP-006 (0.5, 1, 2 mg capsule)
Drug-drug interaction studies -			
In-vivo effects on primary drug:	☐		
In-vivo effects of primary drug:	☐		
Concomitant therapy:	☐		
In-vitro:	☐	4	CC-4047-DMPK-023, CC-4047-DMPK-02, CC-4047-DMPK-037, CC-4047-DMPK-043
Subpopulation studies -			
ethnicity:	☐		
gender:	☐		
pediatrics:	☐		
geriatrics:	☐		
renal impairment:	☐		Planned for 2012
hepatic impairment:	☐		
PD -			
Phase 2:	☐		
Phase 3:	☐		
PK/PD -			
Phase 1/2, proof of concept:	☐		
Phase 3 clinical trial:	☐		
Population Analyses -			
Data rich:	☐		
Data sparse:	☐		
QT evaluation:	☐		
II. Biopharmaceutics			
Absolute bioavailability:	☐		
Relative bioavailability -			
solution as reference:	☐		
alternate formulation as reference:	☐		
Bioequivalence studies -			
traditional design:	☒	2	CC-4047CP-005 (2 mg capsule), CC-4047CP-007 (1, 2, 3, 4 mg capsule)
replicate design:	☐		
Food-drug interaction studies:	☒	1	CC-4047CP-005
Bio-waiver request based on BCS	☐		
BCS class	☒		Class 4
Alcohol induced dose-dumping	☐		
III. Other CPB Studies			
Genotype/phenotype studies	☐		
Chronopharmacokinetics	☐		
Pediatric development plan	☐		
Literature References	☐		
Total Number of Studies			

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			1 mg and 2 mg (from pivotal studies) were used in BE study
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			Analytical assays not provided for metabolites (<10% exposure compared to parent AUC)
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?				
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		X		Sponsor states that there was not sufficient PK data to determine an E-R relationship
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		X		Sponsor plans to continue collecting exposure data to conduct ER
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the		X		Sponsor states that there was not

	label?				sufficient PK data to determine an E-R relationship
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

Is the Clinical Pharmacology Section of the Application Fileable?

☒ **Yes**

☐ **No**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant:

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. Provide the raw datasets and file definitions in electronic format (i.e., SAS transport files) for Study 1398/284 (CDC-407-00-001; MM-001-PK Report). If this information has already been submitted, please provide the location in the eCTD.

2. Confirm that the formulation used in the food effect sub-study in study CC-4047CP-005 was the to-be-marketed formulation.

3. Provide activity of all detected metabolites and any corresponding reports to confirm findings.

Reviewer Note: Based on the sponsors NDA presentation held on 08 June 2012, the following studies are either ongoing or planned

- Renal impaired study (CC-4047-MM-008) is currently ongoing (anticipated completion in 2015)
- Hepatic impaired studies are planned for 4Q 2012
- Clinical DDI studies to assess the influence of CYP3A4, CYP1A2 and P-gp inhibitors on pomalidomide exposure and any metabolites is planned (sponsor did not state initiation date).
- A dedicated QT study to assess pomalidomide potential to prolong QT interval is planned (sponsor did not state initiation date).

Signatures:

Rachelle M. Lubin, Pharm.D.
Reviewer
Division of Clinical Pharmacology 5

Bahru Habtemariam, Pharm.D.
Acting Team Leader
Division of Clinical Pharmacology 5

NDA 204026 Pomalidomide Capsules – PDUFA Action Dates

Product Name		NDA/BLA #	Receipt Date	PDUFA Goal Date	PDUFA Goal Date - Standard
Pomalidomide Capsules		NDA-204026	10-Apr-2012	10-Feb-2013	10-Feb-2013
Activity	**Responsible Party**	**Process Standard**	**Target Date**	**Actual Date**	**Notes/Comments**
Phase 1 - Process Submission, Plan for review, Determine Fileability					
Identify signatory authority	Richard Pazdur, MD	By Day 14	24-Apr-12		
Assign RPM, review team	OND DD & Disciplines Management				
Assign CDTL	Ann T. Farrell, MD				Not yet assigned
Preliminary decision - Review Classification (P/S)	DD, CDTL,RPM				
Schedule Filing Meeting	Amy Baird			May 30, 2012	
Issue Acknowledgement Letter	Amy Baird				
Identify Inspection Actions: EER/PAI/DSI	RPM or primary medical reviewer	By Day 45	25-May-12		
Designate standard/priority review classification:	Ann T. Farrell, MD or Richard Pazdur, MD				
Conduct Filing Review (all reviewers are expected to complete a standard filing review template	Review Team				
Convey potential RTF issues to applicant	RPM facilitates filing meeting, schedules team meetings				
Hold Filing/Planning Meeting a. Make filing decision b. Determine need for consults c. Determine number and approximate time for review team meetings					

d. Determine need for AC meeting and names of SGEs	Review Team				AC to be held at: month 7-8 for standard review/OD signoff; month 7-8.5 for standard review/DD signoff; month 4-5 for priority reviews
e. Establish interim deliverables and dates for completion	Review Team				
Hold (optional) Applicant Orientation Presentation	Review Team	By Day 45	25-May-2012		
Inform applicant of review designation, filing determination	Ann T. Farrell, MD	By Day 60	9-Jun-2012		
Communicate filing review issues and target dates for labeling and PMC discussions to applicant	Amy Baird	By Day 74	23-Jun-2012		
Phase 2 - Conduct Review and Issue Discipline Review Letters					
Hold team meetings (See Activity Summary for meeting information)	RPM to schedule with Review Team	At regular intervals throughout review cycle			
Hold mid-cycle meeting	RPM to schedule Review Team	End of month 5	10-Sep-2012		
Hold team labeling meetings (See Activity Summary for meeting information)	RPM to schedule with Review Team	At regular intervals throughout review cycle			
Complete primary & secondary reviews	Primary	8 weeks before action	16-Dec-2012		
	Secondary	7 weeks before action	23-Dec-2012		
Issue DR letters, as needed.	Review Team	6 weeks before action	30-Dec-2012		
Phase 3 - Action Phase					
Hold wrap-up meeting	RPM to schedule w/ Review Team	8 weeks before action	16-Dec-2012		
Office Director Signature Applications					
Hold internal briefing(s) for OD (as needed)	RPM to schedule/Review Team	As Required			

Complete CDTL Review	Not yet assigned	6 weeks before action	30-Dec-2012		
Send proposed labeling /PMC /PMR/ REMS to applicant with 1 week response	Review Team	7 weeks before action	23-Dec-2012		
Begin Labeling/Post-marketing Commitment/PMR Discussions	Review Team/Applicant	6 weeks before action	30-Dec-2012		
Compile and circulate action letter and action package	Amy Baird	6 weeks before action	30-Dec-2012		
Complete DD review or sign-off	Ann T. Farrell, MD	3 weeks before action	20-Jan-2013		
Action Package & Letter to OD	RPM/Review Team	3 weeks before action	20-Jan-2013		
Complete OD review and sign-0ff	Richard Pazdur, MD	By end of month 10	10-Feb-2013		
Phase 4 - Post Action					
Post decisional meeting w/ Review Team to discuss rationale	Signatory Official	As close to action as possible			
Send action letter (fax or e-mail) to applicant and confirm receipt; notify Press Office if necessary	Amy Baird	Immediately after finalization	10-Feb-2013		
Send approval letter and summary review to FOI	Amy Baird	Within 1 business day after action	11-Feb-2013		
Complete Action Pkg, send to DDR/FOI	Amy Baird	Within 2 business days after action	#NAME?		
Post-Action Feedback Meeting/End of Review Conference	Signatory Official & Review Team	As requested by the applicant			

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

/s/

RACHELLE M LUBIN
06/18/2012

BAHRU A HABTEMARIAM
06/20/2012

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

NDA Number	204-026
Product name, generic name of the active, and dosage form and strength	Pomalidomide, IR capsules, 1, 2, 3, and 4 mg
Submission date	04/10/12
Applicant	Celgene Corporation
Medical Division	Division of Hematology Products
Type of Submission	Original/N-000
Biopharmaceutics Reviewer	Tien-Mien Chen, Ph.D.
Biopharmaceutics Team Leader	Angelica Dorantes, Ph.D.

The following parameters from the ONDQA Quality (CMC and Biopharmaceutics) joint filing checklist are necessary in order to initiate a full Biopharmaceutics review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. BIOPHARMACEUTICS				
	Parameter	**Yes**	**No**	**Comment**
1.	Does the application contain dissolution data?	X		The following dissolution method and acceptance criterion are proposed for routine testing: USP Apparatus II (Paddle) with 50 rpm Q (b) (4) at 45 min
2.	Is the dissolution test part of the DP specifications?	X		The acceptability of the proposed acceptance criterion will be a review issue.
3.	Does the application contain the dissolution method development report?	X		Incomplete; a comment requesting the submission of the complete data will be sent to the Applicant.
4.	Is there a validation package for the analytical method and dissolution methodology?	X		
5.	Does the application include a biowaiver request?		X	
6.	Does the application include an IVIVC model?		X	
7.	Does the application include information/data on in vitro alcohol dose-dumping potential?		X	
8.	Is there any in *vivo* BA or BE information in the submission?	X		BE studies to link 1 and 2 mg to 3 and 4 mg IR capsules

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B. filing conclusion				
	Parameter	**Yes**	**No**	**Comment**
9.	**IS THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**			➢ The NDA is filable from Biopharmaceutics Perspective ➢ The acceptability of the proposed dissolution method and acceptance criteria will be a review issue.
10.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not applicable.
11.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not applicable
12.	Are there any potential review issues identified?		X	A Biopharmaceutics comment requesting the submission of the dissolution development report with complete data supporting the selection of the proposed method will be included in the 74 Day letter.

13.	Are there any comments to be sent to the Applicant as part of the 74-Day letter?	X		1. The provided dissolution information is incomplete, please submit the following; - The complete data supporting the selection of the proposed method. Also include your rationale for the selection of this test. - Include detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (i.e., selection of the equipment/apparatus, in vitro dissolution media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select the proposed dissolution method as the optimal test for your product. Also include the data for the testing conducted to show the discriminating capability of the selected test. 2. Submit the complete dissolution profile data (raw data, mean values, and SD; n=12 capsules) from the clinically tested batches supporting the selection of the dissolution acceptance criterion (i.e., specification-sampling time point and specification value).

{See appended electronic signature page}

Tien-Mien Chen, Ph.D. 06/06/12
Biopharmaceutics Reviewer Date
Office of New Drug Quality Assessment

{See appended electronic signature page}

Angelica Dorantes, Ph.D. 06/06/12
Biopharmaceutics Team Leader Date
Office of New Drug Quality Assessment

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

/s/

TIEN MIEN CHEN
06/07/2012

ANGELICA DORANTES
06/07/2012