CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-880

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics NDA Review

Brand name: REVLIMID®

Generic name: Lenalidomide

Type of dosage form and strength(s): 5 and 10 mg capsules

Indication(s): the Applicant's proposed indication is, "... for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities."

NDA number, type: NDA 21-880, 1P

Applicant name: Celgene Corporation

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1. Executive Summary

A single commitment for clinical pharmacology and biopharmaceutics is recommended.

1.1. Recommendations

This NDA is acceptable from the clinical pharmacology and biopharmaceutics perspective.

1.2. Identify recommended Phase 4 study commitments if the NDA is judged approvable

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

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings (1-3 pages)

Lenalidomide is structurally similar to the teratogenic drug thalidomide.

Following oral administration, maximum lenalidomide plasma concentrations occur from 0.5 - 4 hours post-dose. Co-administration with food does not alter the extent of absorption. Half-life of lenalidomide elimination is approximately 3 hours and the pharmacokinetic disposition of lenalidomide is, at doses up to 10X the recommended clinical dose of 10 mg, linear. Approximately two-thirds of lenalidomide is eliminated unchanged through urinary excretion. The process exceeds the glomerular filtration rate and therefore entails an active component. In mutliple myeloma patients with mild renal impairment, AUCs were 56% higher than in similar patients with normal renal function.

A search for circulating lenalidomide metabolites in human biomaterials (plasma, urine or feces) was not performed.

Results from human *in vitro* metabolism studies show that lenalidomide is not metabolized through the cytochrome P450 pathway. Human *in vitro* metabolism studies also show that lenalidomide does not inhibit or induce cytochromes P450.

The pharmacokinetics of lenalidomide in patients with renal impairment or hepatic impairment have not been systematically studied. The effects of age on the pharmacokinetics of lenalidomide have not been studied. No pharmacokinetic data are available in patients below the age of 18 years. The effects of gender on the pharmacokinetics of lenalidomide have not been studied. Pharmacokinetic differences due to race have not been studied.

Lenalidomide is a BCS Class 3 (high solubility – low permeability) substance. Based on the compositional proportionality of the strengths, the dosing regimen used in clinical trials, pharamacokinetic linearity, and comparative dissolution profiles, the Applicant requests and will be granted a waiver for an in vivo bioequivalence study comparing the 5 mg capsule strength studied in efficacy and safety studies and the 10 mg strength which will be marketed, in addition to the 5 mg strength.

2. *Question-Based Review*

2.1. General attributes of the drug

What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

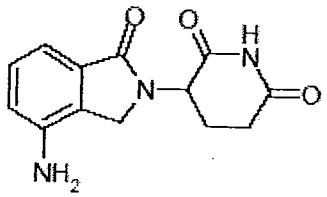
REVLIMID® for the treatment of transfusion dependent MDS (the current indication) has been granted Orphan Drug status.

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?

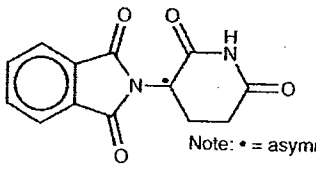
The active ingredient in the drug product is lenalidomide (CC-5013, CDC-501). Its International Union of Pure and Applied Chemistry (IUPAC) name is 3-(4'-amino-1-oxo-1,3-dihydro-2*H*-isoindol-2-yl)piperidine-2,6-dione. a structural representation is shown below as **FDA Figure 1A.** To allow comparisons, a structural representation of thalidomide is included as **FDA Figure 1B.**

FDA Figure 1.

A. Lenalidomide -- Applicant's Section 1.2 from p. 1 of the Quality Overall Summary (Section 2.3.S)



B. Thalidomide – Package insert for THALOMID®



The molecular formula for lenalidomide is $C_{13}H_{13}N_3O_3$ and the molecular weight is 259.25 grams per mole. Lenalidomide has an asymmetric carbon atom and can therefore exist as the optically active forms S(-) and R(+). The drug substance is produced as a racemic mixture with a net optical rotation of zero.

Lenalidomide is generally more soluble in organic than aqueous solvents, but exhibits the greatest solubility in 0.1N HCl buffer with an equilibrium solubility of 18 mg/mL. Solubility was significantly lower in less acidic buffers, ranging from about 0.4 to 0.5 mg/mL.

The dosage form is an opaque hard gelatin capsule; the 5 mg strength is a size 2 capsule and the 10 mg strength is a size 0 capsule. The inactive ingredients of lenalidomide capsules are anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

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

The proposed effects of lenalidomide on biological processes are summarized below. The relationship between lenalidomide's effects on biological processes and its therapeutic effect is unknown.

Lenalidomide inhibits the secretion of pro-inflammatory cytokines including tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β), and IL-6 and IL-12 from lipoprotein polysaccharide stimulated (LPS–stimulated) peripheral blood mononuclear cells (PBMCs). Lenalidomide increases production of the anti-inflammatory cytokine IL-10 from LPS-stimulated PBMC, and consequently inhibits the expression but not the enzymatic activity of cyclooxygenase-2 (COX-2).

Lenalidomide induces T-cell proliferation and IL-2 and IFN-γ production, and augments cytotoxic activity of natural killer cells.

Lenalidomide inhibits the proliferation of various hematopoietic tumor cell lines, in particular those with cytogenetic defects of chromosome 5. Anti-proliferative effects have been observed in MM.1S multiple myeloma[7] and Farage non-Hodgkin's lymphoma cell lines *in vitro*. Lenalidomide inhibits the VEGF-induced clonogenic response and signaling through Akt in KG-1 chromosome 5- acute myeloid leukemia cells. In Namalwa chromosome 5- Burkitt's lymphoma cells, lenalidomide inhibits cell cycle progression and blocks signaling through Gab-1 and Akt.

Lenalidomide induces fetal hemoglobin expression upon $CD34^+$ hematopoietic stem cell differentiation in a model of erythroid progenitor differentiation.

Lenalidomide inhibits angiogenesis by blocking the formation of microvessels and endothelial cell tubes as well as the migration of endothelial cells in *in vitro* angiogenesis

models. Lenalidomide also inhibits production of the pro-angiogenic factor VEGF production by PC-3 prostate tumor cells.

The proposed package insert gives the following indication. "REVLIMID® is indicated for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities."

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

The recommended starting dose of REVLIMID® is 10 mg once daily. A scheme for titrating dose in patients who experience certain hematologic toxicities is included in the package insert and is reproduced below (indent, font change).

> Dose Adjustments During Treatment:
> Patients who are dosed initially at 10 mg and who experience thrombocytopenia that develops **within the first 4 weeks** of starting REVLIMID® therapy should have their dosage adjusted as follows:
>
> - For patients with a baseline platelet count ≥100,000/μL, hold REVLIMID® when the platelet count falls to <50,000/μL. REVLIMID® treatment may be resumed at 5 mg/day when the platelet count recovers to ≥50,000/μL.
> - For patients with a baseline platelet count <100,000/μL, hold REVLIMID® when the platelet count falls by 50% of the baseline value. REVLIMID® treatment may be resumed at 5 mg/day when the platelet count recovers to ≥50,000/μL for patients whose baseline platelet count was ≥60,000/μL and to ≥30,000/μL for patients whose baseline platelet count was <60,000/μL.
>
> Patients who are dosed initially at 10 mg and who experience neutropenia that develops **within the first 4 weeks** of starting REVLIMID® therapy should have their dosage adjusted as follows:
>
> - For patients with a baseline ANC ≥1,000/μL, hold REVLIMID® when the ANC falls to <750/μL. REVLIMID® treatment may be resumed at 5 mg/day when the ANC recovers to ≥1,000/μL.
>
> For patients with a baseline ANC <1,000/μL, hold REVLIMID® when the ANC falls to <500/μL. REVLIMID® treatment may be resumed at 5 mg/day when the ANC recovers to ≥500/μL.
>
> Patients who experience thrombocytopenia after the first 4 weeks of REVLIMID® therapy should have their dosage adjusted as follows:
>
> - If platelet count is < 30,000/μL or platelet count is < 50,000/μL and the patient requires platelet transfusions, hold REVLIMID®. Resume treatment at 5 mg/day when platelet count is ≥ 30,000/μL (without hemostatic failure).
>
> Patients who experience neutropenia after the first 4 weeks of therapy should have their dosage adjusted as follows:
>
> - If ANC is < 500/μL for ≥ 7 days or ANC is < 500/μL associated with fever (temperature ≥ 38.5 °C), hold REVLIMID®. Resume treatment at 5 mg/day when ANC ≥ 500/μL.

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?

Support for the efficacy of lenalidomide for the desired indication comes from 2 studies, Study MDS-501-001 (MDS-001) and Study CC-5013-MDS-003 (MDS-003). The primary study is MDS-003.

MDS-001 was a Phase 1/2, open-label, single-arm, 2-stage, dose-finding study of the safety and efficacy of lenalidomide for the treatment of subjects with MDS. Based on the prior determination that 25 mg/day was the maximum tolerated dose (Study CDC-501-001), the initial starting dose of lenalidomide in this study was 25 mg daily, and the first 13 subjects who were enrolled in the study were treated with this dose. Although erythroid responses were achieved within 16 weeks, a high incidence of neutropenia and thrombocytopenia was observed within the first 4 to 8 weeks of treatment. As a result of these findings, the protocol was amended to study 2 lower-dose regimens in sequential order: 1) a "continuous regimen" in which 10 mg of lenalidomide was administered daily without a planned rest, and 2) a "syncopated" regimen in which 10 mg of lenalidomide was administered on Days 1 through 21 of repeated 28-day cycles. Twelve subjects were treated with the 10-mg continuous regimen, and, although erythroid responses were observed, the median time to dose-limiting neutropenia or thrombocytopenia was found to be 13 weeks. Based on these safety findings, enrollment into the 10-mg syncopated regimen was initiated. After 3 erythroid responses were observed among the first 5 subjects who were treated with the 10-mg syncopated dosing regimen, an additional 15 subjects were enrolled in that group to gain further clinical experience with the syncopated regimen.

Study MDS-003 was a Phase 2, multicenter, open-label, single-arm study of the efficacy and safety of lenalidomide when administered at a dose of 10 mg daily either as a "syncopated" (i.e., administration of 10 mg/day of lenalidomide on Days 1-21 of repeated 28-day cycles) or "continuous" (administration of 10 mg/day of lenalidomide without a planned rest) regimen to subjects with an IPSS diagnosis of low- or intermediate-1-risk MDS and an associated del 5 (q31-33) cytogenetic abnormality (as an isolated finding or associated with other cytogenetic abnormalities) and RBC-transfusion-dependent anemia. Based on preliminary data from the pilot study (Study MDS-001), the first 45 enrolled subjects were treated with the 10-mg syncopated dosing regimen. However, after additional information from the pilot study suggested that the onset of response was more rapid with the 10-mg continuous dosing regimen than with the 10-mg syncopated regimen, without additional safety concerns, the 10-mg continuous dosing regimen was adopted, and 103 subjects were enrolled in the study and treated with the continuous dosing regimen.

Neither Study MDS-001 nor Study MDS-003 was designed or powered to prospectively compare the efficacy of the lenalidomide regimens. A comparison of the outcomes

associated with the "syncopated" and "continuous" regimens in Study MDS-003 is shown in the Applicant's Table 13 which is reproduced below as **FDA Table 1.**

FDA Table 1. Applicant's Table 13 from p. 28 of the Summary of Clinical Efficacy (Section 2.7.3)

Table 13. Summary of Efficacy Variables by Initial Lenalidomide Regimen and Overall in Study MDS-003 (MITT Population)

Efficacy Parameter[a]	10 Cont	10 Sync	Overall
RBC-transfusion Independence[b]	65.1% (41/63)	51.6% (16/31)	60.6% (57/94)
Median Change From Baseline in Hemoglobin at Maximum Value During Response Period	5.6	5.4	5.5
≥50% Reduction in Pretreatment RBC Transfusion Requirements	73.0% (46/63)	71.0% (22/31)	72.3% (68/94)
Cytogenetic Response[c] Major Minor	26.7% (12/45) 37.8% (17/45)	43.5% (10/23) 21.7% (5/23)	32.4% (22/68) 32.4% (22/68)

Data Source: Study MDS-003, Table 14.2.1.3, Table 14.2.4.3, 14.2.1.6, and Table 14.2.6.3

[a] Results represent data available as of the 15 September 2004 data cutoff date.

[b] The absence of any RBC transfusion during any consecutive rolling 56 days in the evaluation period and an increase in hemoglobin of at least 1 g/dL from the minimum during the 56 days prior to the maximum during the transfusion-independent period, excluding the first 30 days after the last transfusion before the transfusion-free period.

[c] Based on subjects who were evaluable for cytogenetic response at baseline (i.e., those who had at least 20 analyzable metaphases at baseline when using conventional cytogenetic techniques. Major response = no detectable cytogenetic abnormality if a preexisting abnormality was present. Minor response = ≥50% reduction in the percent of abnormal metaphases.

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

The primary efficacy endpoint in Study MDS-003 is RBC-transfusion independence, defined as the absence of any intravenous RBC transfusion during any consecutive 56 days during the treatment period accompanied by at least a 1 g/dL increase from screening/baseline in Hgb. The primary efficacy endpoint of RBC-transfusion independence and the secondary efficacy endpoints of the frequency of subjects with a ≥50% decrease from baseline in RBC transfusion requirements, platelet response, neutrophil response, bone marrow response, cytogenetic response, and duration of transfusion independence were assessed based on the criteria set forth by the MDS International Working Group (IWG) (Cheson et al, 2000). The change from baseline in Hgb concentration (which is not required by IWG criteria for the assessment of transfusion independence) was added as an additional criterion for response to further quantify and confirm transfusion independence.

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?

The performance of the bioanalytical methods will be reviewed in Section 2.6.

The NDA has no data regarding a search for the presence of metabolites in human matrices *ex vivo*. Twenty-one - 43% of an administered dose of 5 - 20 mg was not excreted in urine over a 48 hour period (see Section 2.2.5.7). The fate of the un-recovered dose (e.g., excretion in feces prior to or subsequent to absorption, excretion in urine as metabolites, or extended residence in tissues) is unknown. Thus, unidentified metabolites may be present.

Lenalidomide is structurally similar to thalidomide. Administration of thalidomide is known to result in circulating thalidomide-derived moieties. The activity of these moieties is not known.

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for *efficacy*? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

Clinical studies assessing the relationship between exposure and efficacy were not performed. The basis of the proposed package insert dosing recommendations is presented in Section 2.2.1. Pharmacokinetics data were not collected in Study MDS-001. Except for the drug interaction sub-study, pharmacokinetics data were not collected in Study MDS-003.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for *safety*? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

Clinical studies assessing the relationship between exposure and safety were not performed. The basis of the proposed package insert dosing recommendations is presented in Section 2.2.1. Pharmacokinetics data were not collected in Study MDS-001. Except for the drug interaction sub-study, pharmacokinetics data were not collected in Study MDS-003.

2.2.4.3 Does this drug prolong the QT or QTc interval? *(You must answer this question, unless this is addressed in the question above.)*

Neither a thorough QTc study nor a pilot study designed to assess any effects of lenalidomide on QT-interval were performed.

A search for the letters "qt" in the Summary of Clinical Safety identifies three occurrences, all of which are part of the same sentence. The sentence is part of the summary for study 1398/180 (A Phase I, single-blind, placebo-controlled, oral dose, safety, tolerability, pharmacodynamic and pharmacokinetic study in healthy, male subjects), and is reproduced below (indent, font change).

> "ECGs were reviewed by an independent cardiologist who reported no conclusive effect of lenalidomide (CC-5013) in prolonging QTc and no clinically significant prolongation of QT or QTc interval throughout the study."

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?

The relationship between dose-concentration and response is largely unknown. The currently recommended 10 mg dose requires frequent dose reductions (approximately 80% of patients), suggesting that higher doses are not prudent. The efficacy of lower doses is unknown. Determination of an optimal dose is an unresolved dosing issue.

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? *(Provide tables to refer to in subsequent questions in this section.)*

FDA Table 2. (Applicant's Table 12., following page) summarizes the pharmacokinetics of lenalidomide. **FDA Figures 2. and 3.** (Applicant's Figures 8. and 9., following **FDA Table 2.**) show concentration-time profiles following single and multiple doses.

On both the first day and 28 days after once daily dosing of 5 – 50 mg, plasma concentrations reached a maximum at 1.0 to 1.5 hours post-dose. The elimination half-life of lenalidomide (CC-5013) ranged from 3 to 4 hours on Days 1 and 28 at all doses. As would be predicted from the single dose pharmacokinetics, there was no observable accumulation of the drug in plasma upon multiple dosing. AUC0-oo and Cmax increased in a dose-proportional manner over the dose-range of 5 to 50 mg. No time- or dose-dependency in the pharmacokinetics of lenalidomide was observed.

FDA Table 2. Applicant's Table 12 from page 26 of the Summary of Clinical Pharmacology Studies

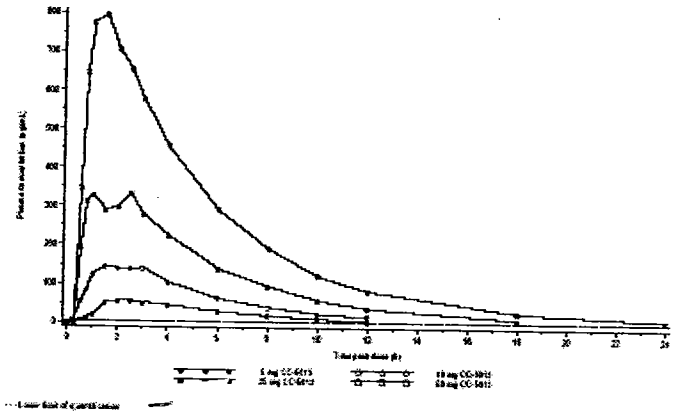
Table 12: PK Parameters After Doses of 5-50 mg, Single and Multiple Doses in Multiple Myeloma Patients

	Dose of CC-5013 to Relapsed Multiple Myeloma Patients (CDC-501-001)							
	5 mg/day		10 mg/day		25 mg/day		50 mg/day	
Parameter	Day 1 (N=3)	Day 28 (N=2)	Day 1 (N=7)	Day 28 (N=5)	Day 1 (N=3)	Day 28 (N=2)	Day 1 (N=14)	Day 28 (N=11)
$AUC_{(0-\tau)}$ (ng·h/mL)	372 (5.57)	373 (15.2)	1614 (56.8)	922 (24.5)	2231 (21.9)	NC	4626 (41.7)	4610 (25.7)
$AUC_{(0-t_n)}$ (ng·h/mL)	359 (5.42)	NA	988 (58.6)	NA	2215 (22.6)	NA	4625 (41.8)	NA
$AUC_{(0-\infty)}$ (ng·h/mL)	382 (5.77)	NA	1046 (63.1)	NA	2262 (23.5)	NA	4688 (42.3)	NA
C_{max} (ng/mL)	72.1 (21.0)	65.0 (62.8)	216 (25.2)	178 (29.6)	522 (13.5)	NC	991 (16.9)	957 (19.2)
t_{max}* (h)	1.50 (1.50-4.00)	1.00 (0.750-6.00)	1.00 (0.500-4.00)	1.50 (0.750-4.00)	1.00 (0.417-2.50)	NC (1.00-1.00)	1.00 (0.500-1.50)	1.50 (0.500-2.50)
$C_{max,ss}$ (ng/mL)	NC	NC	NC	NC	NC	NC	10.7 (74.8)	13.7 (40.5)
$AUC_{(0-\tau)}$ (norm)	6648 (6.22)	6672 (20.0)	7610 (47.1)	7311 (18.3)	7803 (15.6)	NC	7872 (42.6)	7832 (25.2)
$AUC_{(0-\infty)}$ (norm)	6835 (5.02)	NA	7845 (53.2)	NA	7916 (16.8)	NA	7994 (43.3)	NC
C_{max} (norm)	1289 (25.8)	1162 (69.2)	1620 (14.9)	1412 (23.2)	1822 (26.4)	NC	1687 (19.0)	1625 (17.5)
$C_{max,ss}$ (norm)	NC	NC	NC	NC	NC	NC	20.3* (63.8)	23.2 (48.2)
$t_{\frac{1}{2}}$ (h)	2.98 (11.4)	3.08 (14.9)	3.18 (42.5)	3.04 (21.9)	3.36 (23.4)	NC	4.05 (33.2)	3.95 (11.5)
MRT (h)	5.52 (19.8)	NC	5.27 (46.2)	5.46 (19.2)	5.25 (33.8)	NC	5.56 (21.7)	5.75 (13.3)
CL/F (mL/min)	238 (5.77)	NC	159 (63.1)	181 (24.5)	184 (23.5)	NC	177 (42.3)	181 (25.7)
V_z/F (L)	56.3 (13.8)	NC	43.9 (22.7)	47.6 (8.17)	53.6 (1.50)	NC	62.2 (27.3)	61.8 (24.7)
RA_1	1.03* (1.68)	1.00 (19.2)	1.01* (0.465)	1.09 (22.4)	NC	NC	1.01* (0.817)	1.07 (12.1)
RA_2	1.03* (1.68)	0.903 (40.2)	1.01* (0.465)	0.892 (12.0)	NC	NC	1.01* (0.817)	0.979 (14.2)
RL	NA	0.976 (20.3)	NA	1.08 (22.7)	NA	NC	NA	1.05 (12.6)

Geometric mean (CV%) data are presented, * Median (min-max). N = Number of patients studied (* N=13)
* Predicted value (mean based on values for patients completing Day 28 only)
(norm) = Normalized for dose and body weight (mg/kg)
NC = Not calculable
NA = Not applicable
τ = 24 hours
RA_1 = Accumulation ratio based on AUC
RA_2 = Accumulation ratio based on C_{max}
RL = Linearity ratio = AUC(0-τ) (Day 28)/AUC(0-∞) (Day 1)

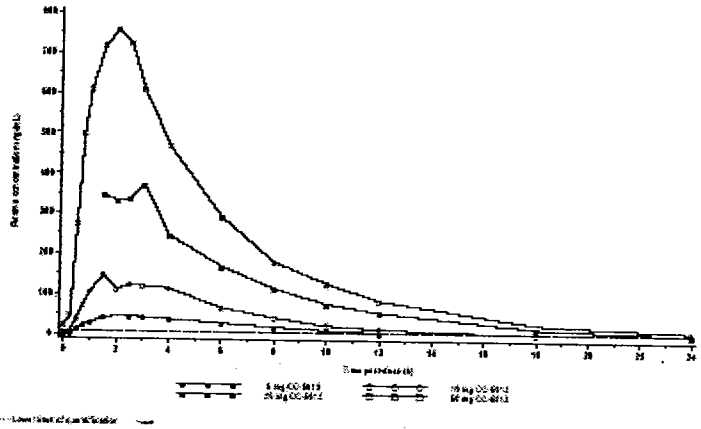
FDA Figure 2. Applicant's Figure 8. from page 27 of the Summary of Clinical Pharmacology Studies

Figure 8: Day 1 Geometric Mean Plasma Concentrations of lenalidomide (CC-5013)



FDA Figure 3. Applicant's Figure 9. from page 27 of the Summary of Clinical Pharmacology Studies

Figure 9: Day 28 Geometric Mean Plasma Concentrations of lenalidomide (CC-5013)



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

FDA Table 3. (below) compares the pharmacokinetics of lenalidomide in healthy subjects and patients.

FDA Table 3. Comparison of PK parameters in healthy subjects and patients receiving single doses of 5 - 50 mg

	1398/142 = healthy	PK-003 = healthy	1398/271 (001) = patients	% change (healthy compared to patients)
	5 - 50 mg, n=17	10 mg, n=17	5 - 50 mg, n=27	
CL/F (mL/min)	287	289	178	+62
t1/2 (h)	3.4	2.6	3.6	-17
Vz/F (L)	86	not reported	56	+54

Clearance was 62% greater in healthy subjects than in patients, similarly, t1/2 was reduced (17%) in healthy subjects. The Applicant conducted an analysis of the differences between healthy subjects and patients receiving single 100 mg doses. The results are shown below (**FDA Table 4.**). As indicated in the table, the Applicant attributes the differences between the populations as due to differences in renal function and age between the groups.

FDA Table 4. Applicant's Table 13 from page 29 of the Summary of Clinical Pharmacology Studies

Table 13: Comparison between single oral 100 mg doses from studies 1398/142 and1398/180 in healthy subjects and CDC-501-001 in relapsed multiple myeloma patients

PK Parameter	CC-5013 1398/142 N = 6 Healthy Volunteers	CC-5013 1398/180 (Day 1, single dose) N = 6 Healthy Volunteers	CDC-501-001 (Day 1, single dose 50 mg Adjusted to 100 mg for AUC & Cmax) Older, relapsed MM patients
Age (yrs.)	29	29	58
AUC $_{0-\infty}$ [ng•h/ml]	5997 ± 18%	6006 ± 20%	9400 ± 42%
Cmax [ng/ml]	1735 ± 46%	1618 ± 33%	1982 ± 17%
t_{max} [hr] median	1.5 (range: 1-1.5)	1.0 (range 0.5-2)	1.0 (range 0.5-1.5)
t-1/2 [hr^{-1}]	4.7 ± 33%	3.5 ± 4.9%	4.0 ±33%
Cl/F [ml/min]	278 ± 18%	277 ± 20%	177 ± 42%*

*The decreased clearance in relapsed multiple myeloma patients is related to the age-associated decrease in clearance of the older patients compared to the younger, healthy subjects.

2.2.5.3 What are the characteristics of drug absorption?

Lenalidomide is highly hydrophilic, but showed low permeability in the Caco-2 system. More consistent with its lipophilicity, lenalidomide showed high permeability in the PAMPA system. The discrepancy between the systems is unknown, but potentially could be explained by a difference in the presence of transporters or differences in membrane structure. Consistent with the Caco-2 data, the Applicant classifies lenalidomide as a low permeability substance.

2.2.5.4 What are the characteristics of drug distribution? *(Include protein binding.)*

Values for the volume of distribution appear in **FDA Table 3.** of this document. Mean plasma protein binding was 23%, in human subjects with multiple myeloma and 29% in healthy human volunteers.

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

A mass balance study was not conducted. Excretion results, which will be discussed in section 2.2.5.7, identify renal elimination of parent as the primary route of elimination.

2.2.5.6 What are the characteristics of drug metabolism? *(This may include data on extraction ratio; metabolic scheme; enzymes responsible for metabolism; fractional clearance of drug.)*

In *in vitro* studies using non-radio-labeled lenalidomide, there was no clear signal that lenalidomide metabolism occurred in human liver microsomes. Similarly, there was no clear evidence of significant metabolism of lenalidomide by cDNA expressed human P450 isoenzymes in Supersomes.

In order to confirm the results of the non-radiolabelled studies, duplicate studies were performed using radiolabelled lenalidomide. In pooled human liver microsomes there was no *in vitro* metabolism of lenalidomide at a protein concentration of 1 mg/mL after 10 or 60 minutes of exposure. Similarly, after a 60 minute incubation with Supersomes. (100 pmol P450/mL), there was no evidence of lenalidomide (10 µM) metabolism. It was concluded that lenalidomide was resistant to Phase I metabolism.

In isolated human hepatocytes [^{14}C]-lenalidomide was added to yield final concentrations of 1, 5, and 25 µM and incubations at 37°C were performed for 0, 1, 2, 4, or 6 hours. Both negative controls (without hepatocytes) and positive controls (with [^{14}C]-7-Ethoxycoumarin) were used in this experiment. There was no metabolism of lenalidomide after 6 hours of exposure. It was concluded that lenalidomide was resistant to both Phase I and Phase II metabolism.

While excretion in urine failed to recover as much as 43% of the administered dose (see Section 2.2.5.7.), there is no data measuring lenalidomide metabolites in human matrices *ex vivo* or following incubation with human biomaterial *in vitro*.

Following oral and intravenous administration of [^{14}C]-lenalidomide to cynomolgus monkeys, the primary metabolic pathway was by hydrolysis of the piperidine dione ring which formed two isomeric hydrolysis products. The urine and feces both contained ring-hydrolyzed compounds as well as significant proportions of unchanged drug (23%-53% of the administered dose in urine; up to 28% of the dose in feces). Minor metabolites identified in the feces included 2 glucose conjugates; N-acetyl lenalidomide, a hydroxylated metabolite, and a N-dehydrogenated metabolite.

Following oral administration to rats, the main compound identified in plasma was parent compound and the main metabolites were isomers of a hydrolysis product of lenalidomide. The major component in urine and feces was the parent compound, but hydrolysis metabolites, N-acetyl conjugate isomers, and glucose conjugate isomers of lenalidomide were also present.

2.2.5.7 What are the characteristics of drug excretion?

Neither a mass balance study nor measurement of drug or drug-derived moieties in feces has been performed.

In healthy male subjects receiving 5 or 20 mg of REVILMID, 57 – 79% of the dose was recovered as parent in urine within 48 h (**FDA Table 5.**). Nearly all of the recovery occurred in the first 24 h (all of the 12 subjects excreted < 1.5% of the dose during the 24 h period from 24 h to 48 h).

FDA Table 5. % dose excreted in urine; n = 11 (n = 6 @ 5 mg, n = 5 @ 20 mg)	
0 - 48 h	**24 - 48 h**
56.8 - 78.8	0.6 - 1.4

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

The Applicant's Figures A. and B. from page 62 of the study report for study 1398/142 and Table M. from page 64 of the same report summarize the pharmacokinetics in healthy subjects receiving single doses up to 400 mg. They are reproduced below as **FDA Figure 4.** and **FDA Table 6.**

FDA Figure 4. Applicant's Figures A. and B. from page 62 of the study report for study 1398/142.

Figure A: Geometric Mean Plasma Concentrations of CC-5013 (Fasted) (Linear Scale)

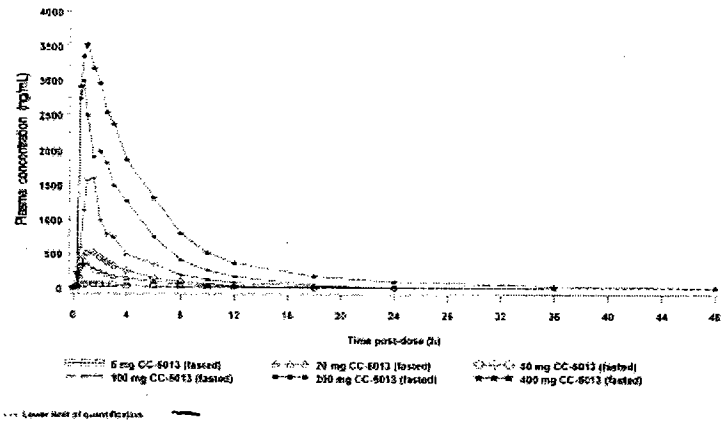
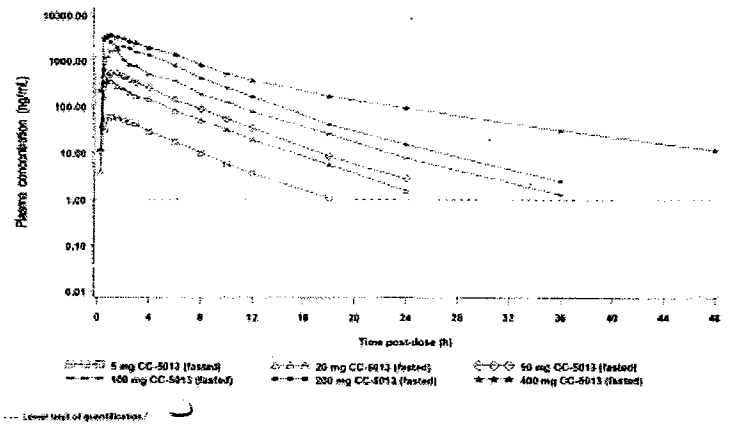


Figure B: Geometric Mean Plasma Concentrations of CC-5013 (Fasted) (Semi-logarithmic Scale)



FDA Table 6. Applicant's Table M from page 64 of the study report for study 1398/142.

Table M: Summary of Plasma Pharmacokinetic Parameter Values of CC-5013 (Fasted)

	Dose of CC-5013 (fasted)					
Parameter	5 mg (N=6)	20 mg (N=6)	50 mg (N=5)	100 mg (N=6)	200 mg (N=6)	400 mg (N=6)
AUC(0-24 h) (ng.h/mL)	314 (9.83)	1380 (14.1)	2530 (31.2)	5936 (18.5)	11999 (36.2)	20385 (12.4)
AUC(0-t_z) (ng.h/mL)	267 (24.1)	1377 (13.9)	2535 (31.6)	5983 (18.2)	12095 (36.4)	21512 (9.98)
AUC(0-∞) (ng.h/mL)	276 (23.7)	1391 (14.0)	2546 (31.4)	5997 (18.2)	12111 (36.4)	21895 (9.08)
C_{max} (ng/mL)	66.2 (14.8)	373 (41.3)	808 (32.8)	1735 (45.9)	3519 (24.5)	4586 (57.4)
t_{max}† (h)	0.875 (0.50-2.00)	0.875 (0.75-2.00)	0.750 (0.50-1.50)	1.50 (1.00-1.50)	0.625 (0.50-2.00)	0.875 (0.50-3.00)
AUC(0-24 h) (norm) (kg.h/mL)	0.799 (11.9)	0.822 (17.5)	0.645 (39.3)	0.767 (32.0)	0.706 (48.4)	0.666 (16.6)
AUC(0-t_z) (norm) (kg.h/mL)	0.630 (34.4)	0.820 (17.3)	0.646 (39.7)	0.773 (31.6)	0.712 (48.6)	0.702 (17.9)
AUC(0-∞) (norm) (kg.h/mL)	0.651 (34.1)	0.828 (17.5)	0.649 (39.5)	0.775 (31.6)	0.713 (48.6)	0.715 (19.1)
C_{max} (norm) (kg/mL)	0.156 (18.8)	0.225 (42.0)	0.206 (39.1)	0.224 (61.0)	0.207 (37.3)	0.150 (59.2)
t½ (h)	3.24 (25.3)	3.66 (5.65)	3.46 (11.8)	4.71 (33.2)	5.16 (30.2)	8.72 (46.9)
MRT (h)	4.61 (15.3)	4.66 (9.72)	4.40 (17.7)	4.66 (17.3)	4.69 (11.9)	7.53 (38.1)
CL/F (mL/min)	302 (23.7)	240 (14.0)	327 (31.4)	278 (18.2)	275 (36.4)	304 (9.08)
CL/F (mL/min/kg)	3.56 (18.8)	2.85 (11.9)	4.13 (27.8)	3.59 (15.6)	3.24 (29.0)	3.98 (20.6)
V_z/F (L)	84.6 (12.3)	76.0 (15.8)	98.1 (21.2)	113 (46.9)	125 (28.6)	230 (48.4)
V_z/F (L/kg)	0.997 (17.2)	0.905 (14.6)	1.25 (21.0)	1.46 (39.9)	1.45 (31.4)	3.00 (63.4)

Source: Section 9.4 (Table 20)
Geometric mean (CV%) data are presented
† Median (min-max)
N = Number of subjects studied
norm = Normalised for dose and body weight (ng/kg)

The concentration-time profiles pharmacokinetics were not "simple" in that secondary peaks were observed for some subjects at all dose levels. In the majority of subjects, the first peak was the maximum plasma level attained (Cmax). Following the occurrence of peak concentrations, plasma levels declined in a multi-phasic manner. At higher doses, plasma levels remained quantifiable for a longer period of time (median terminal-phase half-life at 5 mg was 18 h compared to 48 h at 400 mg). The Applicant suggests that the apparent dose-related increases in terminal elimination half-life is due to the elimination phase being more accurately described due to the longer period over which concentrations could be measured. Thus, the Applicant concludes that the true elimination half-life is likely that seen at the highest dose (400 mg): approximately 9 h.

Without a more sophisticated analysis of linearity, the Applicant's conclusion can neither be affirmed nor denied. As the recommended dose for REVILMID is 10 mg, if non linearity occurs, it is at doses ≥ 10X the recommended dose, and thus is not a clinical issue.

2.2.5.9 How do the PK parameters change with time following chronic dosing? *(This may include time to steady-state; single dose prediction of multiple dose PK; accumulation ratio.)*

The Applicant's Table 12 presents pharmacokinetics results across 28 days of dosing. This Table appears as **FDA Table 7.** in an earlier section of this review. For convenience, it is reproduced below.

FDA Table 7. Applicant's Table 12 from page 26 of the Summary of Clinical Pharmacology Studies

Table 12: PK Parameters After Doses of 5-50 mg, Single and Multiple Doses in Multiple Myeloma Patients

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Parameter	Dose of CC-5013 to Relapsed Multiple Myeloma Patients (CDC-501-001)							
	5 mg/day		10 mg/day		25 mg/day		50 mg/day	
	Day 1 (N=3)	Day 28 (N=3)	Day 1 (N=7)	Day 28 (N=5)	Day 1 (N=3)	Day 28 (N=2)	Day 1 (N=14)	Day 28 (N=13)
$AUC_{(0-\tau)}$ (ng·h/mL)	372 (5.57)	373 (15.2)	1014 (56.8)	922 (24.5)	2231 (21.9)	NC	4626 (41.7)	4610 (25.7)
$AUC_{(0-t_z)}$ (ng·h/mL)	330 (5.42)	NA	988 (38.5)	NA	2215 (22.6)	NA	4623 (41.8)	NA
$AUC_{(0-\infty)}$ (ng·h/mL)	382 (5.77)	NA	1046 (63.1)	NA	2252 (25.5)	NA	4698 (42.3)	NA
C_{max} (ng/mL)	72.1 (21.0)	65.0 (62.8)	215 (25.2)	178 (29.6)	523 (13.5)	NC	991 (16.9)	957 (19.2)
t_{max}* (h)	1.50 (1.50-4.00)	1.00 (0.750-6.00)	1.00 (0.500-4.00)	1.50 (0.750-4.00)	1.00 (0.417-2.50)	NC (1.00-1.00)	1.00 (0.500-1.50)	1.50 (0.500-2.50)
$C_{max,ss}$ (ng/mL)	NC	NC	NC	NC	NC	NC	10.7 (74.8)	15.7 (40.5)
$AUC_{(0-\tau)}$ (ncem)	6648 (6.22)	6672 (20.0)	7610 (47.1)	7311 (15.3)	7803 (15.6)	NC	7872 (42.6)	7832 (25.2)
$AUC_{(0-\infty)}$ (ncem)	6833 (5.02)	NA	7845 (53.2)	NA	7910 (16.8)	NA	7994 (43.3)	NC
C_{max} (ncem)	1289 (25.8)	1162 (69.2)	1620 (14.9)	1412 (22.2)	1822 (26.4)	NC	1687 (19.0)	1625 (17.3)
$C_{max,ss}$ (ncem)	NC	NC	NC	NC	NC	NC	20.3* (63.8)	25.2 (48.1)
t_z (h)	2.98 (11.4)	3.08 (14.9)	3.18 (42.5)	3.04 (21.9)	3.56 (25.4)	NC	4.05 (33.2)	3.95 (11.5)
MRT (h)	5.52 (19.8)	NC	5.27 (46.2)	5.46 (19.2)	5.25 (33.8)	NC	5.56 (21.7)	5.75 (13.3)
CL/F (mL/min)	218 (5.77)	NC	159 (63.1)	181 (24.5)	184 (25.5)	NC	177 (42.3)	181 (25.7)
V_z/F (L)	56.3 (13.8)	NC	43.9 (22.7)	47.6 (8.17)	53.6 (1.50)	NC	62.2 (37.3)	61.8 (24.7)
RA_1	1.03* (1.68)	1.00 (19.2)	1.01* (0.465)	1.09 (22.4)	NC	NC	1.01* (0.817)	1.07 (12.1)
RA_2	1.03* (1.68)	0.902 (40.2)	1.01* (0.465)	0.892 (12.0)	NC	NC	1.01* (0.817)	0.979 (14.1)
RL	NA	0.976 (20.3)	NA	1.08 (22.7)	NA	NC	NA	1.05 (12.6)

Geometric mean (CV%) data are presented, * Median (min-max). N = Number of patients studied (* N=13)
' Predicted value (mean based on values for patients completing Day 28 only)
(ncem) = Normalized for dose and body weight (mg/kg)
NC = Not calculable
NA = Not applicable
τ = 24 hours
RA_1 = Accumulation ratio based on AUC
RA_2 = Accumulation ratio based on C_{max}
RL = Linearity ratio = AUC(0-τ) (Day 28)/AUC(0-∞) (Day 1)

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?

Repeated dosing with the intent of determining intra-individual variability was not performed by the Applicant. Study CC-5013-PK-003 (a drug interaction study of the effect of 10 mg lenalidomide QD on the pharmacokinetics of warfarin) includes pharmacokinetic sampling of lenalidomide on two occasions in the same individuals. No effect of warfarin on the pharmacokinetics of lenalidomide was observed in this study. The mean intra-individual %CV between the two occasions was 18% for lenalidomide AUC and 9% for lenalidomide Cmax.

The interindividual variability in PK parameters, across doses and with single and multiple dosing, is reported in **FDA Table 7.** in section 2.2.5.9, above.

Renal function and age may be major causes of pharmacokinetic variability in patients. This will be discussed in section 2.3.2.5.

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?

No formal studies have been conducted to assess the effects of age, gender, race, size, genetic polymorphism, pregnancy or organ dysfunction on the pharmacokinetics of lenalidomide. The relationship between exposure and efficacy and safety is largely unknown.

The Applicant's Table 13 is reproduced below as **FDA Table 8**. Note that the dose is 100 mg: 10X the recommended clinical dose.

FDA Table 8. Applicant's Table 13 from page 29 of the Summary of Clinical Pharmacology Studies

Table 13: Comparison between single oral 100 mg doses from studies 1398/142 and1398/180 in healthy subjects and CDC-501-001 in relapsed multiple myeloma patients

PK Parameter	CC-5013 1398/142 N = 6 Healthy Volunteers	CC-5013 1398/180 (Day 1, single dose) N = 6 Healthy Volunteers	CDC-501-001 (Day 1, single dose 50 mg Adjusted to 100 mg for AUC & Cmax) Older, relapsed MM patients
Age (yrs.)	29	29	58
AUC $_{0-\infty}$ [ng.h/ml]	5997 ± 18%	6006 ± 20%	9400 ± 42%
Cmax [ng/ml]	1735 ± 46%	1618 ± 33%	1982 ± 17%
t_{max} [hr] median	1.5 (range: 1-1.5)	1.0 (range 0.5-2)	1.0 (range 0.5-1.5)
t-1/2 [hr^{-1}]	4.7 ± 33%	3.5 ± 4.9%	4.0 ±33%
Cl/F [ml/min]	278 ± 18%	277 ± 20%	177 ± 42%*

*The decreased clearance in relapsed multiple myeloma patients is related to the age-associated decrease in clearance of the older patients compared to the younger, healthy subjects.

As stated in the table's footnote, the Applicant attributes the 56% decrease in clearance in patients relative to healthy subjects to the difference in age and renal status between the groups. While the Applicant's conclusion is not unreasonable, it is not supported by data – there is no pharmacokinetics data from healthy volunteers that were elderly or renally impaired.

The Applicant's subgroup analyses show that achievement of RBC-transfusion independence is not affected by age, gender, ECOG performance status, FAB classification, or IPSS classification, suggesting that no dosage adjustments are needed based on demographic or prognostic factors.

Significantly more subjects > 65 years of age (42.1%; 120/285) than ≤ 65 years of age (28.2%; 31/110) had at least one serious adverse event ($p \leq 0.05$; Fisher's Exact Test). Neutropenia was reported as a serious adverse event significantly more frequently in subjects >65 years of age (4.2%; 12/285) than in those ≤ 65 years of age (0%; 0/110) ($p \leq 0.05$; Fisher's Exact Test). The frequency of other serious adverse events was not significantly different between age groups.

No significant difference was observed between males (38.0%; 79/208) and females (38.5%; 72/187) in the percentage of subjects who had at least one serious adverse event. Deep vein thrombosis was reported as a serious adverse event significantly more frequently in females (2.1%; 4/187) than in males (0%; 0/208) ($p \leq 0.05$; Fisher's Exact Test). No other significant differences were observed.

The number of non-white subjects (21 vs. 374 white subjects) is too small to allow for an evaluation of the effects of race on the frequency of any individual serious adverse event.

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 (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

The clinical study upon which approval will be based used a single starting dose of 10 mg. Dose escalation for patients that tolerated 10 mg was not part of the study design. The study did include dose reductions to 5 mg for patients that did not tolerate 10 mg, and the proposed package insert includes directions on how to reduce dose. Thus, it would appear unlikely that doses higher than 10 mg can be routinely recommended. The effectiveness of starting doses lower than 10 mg is unknown. Thus, in the absence of pharmacokinetic data indicating that a demographic group or sub-population has lower plasma concentrations that those that occurred in patients administered 10 mg QD, it would appear unlikely that doses lower than 10 mg can be routinely recommended.

2.3.2.1 Elderly

No dosage regimen adjustments are recommended.

2.3.2.2 Pediatric patients. Also, what is the status of pediatric studies and/or any pediatric plan for study?

We are unsure of the Applicant's plans for studying pediatric patients. A waiver for pediatric studies has not been granted.

2.3.2.2 Gender

No dosage regimen adjustments are recommended.

2.3.2.4 Race

No dosage regimen adjustments are recommended.

2.3.2.5 Renal impairment

As very little data in renally impaired subjects has not been collected, we cannot make recommendations for dosage regimen adjustments. The following language (indent, font change) is reproduced from the "**Precautions – Geriatric Use**" section of the Applicant's Proposed Package Insert

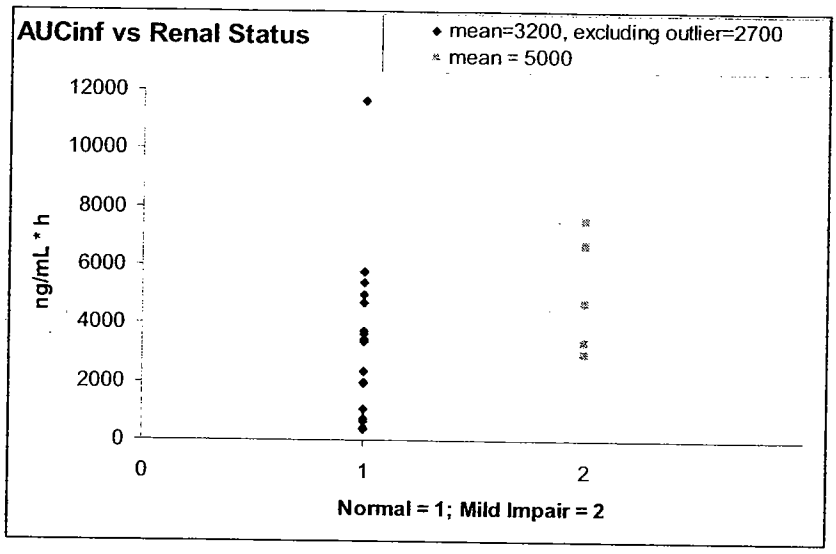
> This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it ___ to monitor renal function.

We recommend that a similar statement regarding monitoring of patients with renal impairment be added to the package insert:

> **PRECAUTIONS**
> **Renal Impairment**
> This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug is expected to be greater in patients with impaired renal function.

Four patients with mild renal impairment were sampled for pharmacokinetics in Study MDS-001. Their AUCs are compared to those of patients in MDS-001 with normal renal function in **FDA Figure 5.**, below. If the apparent outlier in the "Normal" renal function group is excluded, the mild renal impairment group has an AUC 85% greater than the unimpaired group. If the "outlier" is included, the difference is 56%.

FDA Figure 5. The Effect of Mild Renal Impairment on AUC of Lenalidomide



Based on the data showing that 2/3 of lenalidomide is excreted renally (Section 2.2.5.7), and consistent with the apparent effect of renal impairment shown in **Figure 5.**, above, we recommend a Phase 4 commitment to perform a pharmacokinetic study in subjects with renal impairment.

2.3.2.6 Hepatic impairment

No dosage regimen adjustments are recommended.

2.3.2.7 What pharmacogenetics information is there in the application and is it important or not?

The presence of del 5 (q31-33) cytogenetic abnormality was an inclusion criteria for study entry. Other pharmacogenomic information is not included in the application.

A total of 45 subjects were enrolled in Study MDS-501-001 of whom 43 had the protocol-specified diagnosis of MDS with or without an associated del 5 (q31-33) cytogenetic abnormality (2 of the subjects had a diagnosis of Philadelphia chromosome-negative chronic myeloid leukemia and, therefore, were excluded from the analyses). The major erythroid response rate was 44.2% (19/43) and the minor erythroid response rate was 7.0% (3/43) across the 3 lenalidomide regimens that were tested; all of the responses were observed in subjects who had low- or intermediate-1-risk MDS. Subjects with a del 5 (q31-33) cytogenetic abnormality appeared to be particularly responsive to lenalidomide: The major erythroid response rate was 69.2% (9/13) in this population and was associated with a median increase of 5.3 g/dL in Hgb and with major cytogenetic responses in 84.6% (11/13) of the subjects. Responses were observed both with the 10-mg continuous and 10-mg syncopated regimens. Based on the preliminary results of this pilot study, further evaluation of the efficacy and safety of lenalidomide in subjects with low- or intermediate-1-risk MDS with (Study MDS-003) or without (Study MDS-002) an associated del 5 (q31-33) cytogenetic abnormality was instituted.

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

There is no pregnancy and lactation use information in the application.

2.3.2.9 Are there other human factors that are important to understanding the drug's efficacy and safety?

The application does not describe any "other human factors" that are important to understanding the drug's efficacy and safety.

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?

With the exception of food, no studies were conducted to assess correlations between extrinsic factors and the PK profiles or derived parameters for lenalidomide. Patient data with respect to alcohol usage and smoking was not systematically collected during the PK or clinical studies.

2.4.1.1 Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

No dosage regimen changes are recommended.

2.4.2 Drug-drug interactions

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

No. Section 2.2.5.6 discusses the inability of CYP P450 enzymes to metabolize lenalidomide and Section 2.4.2.3 discusses the inability of lenalidomide to inhibit CYP P450 enzymes.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Section 2.2.5.6 discusses the inability of CYP P450 enzymes to metabolize lenalidomide. There is no data indicating that metabolism is influenced by genetics.

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

The potential inhibitory effects of lenalidomide on CYP450 enzyme activity were investigated in human liver microsomes. The following enzyme markers were used in this study: ethoxyresorufin O-dealkylase (EROD) for CYP1A2, tolbutamide methyl-hydroxylase for CYP2C9, S-mephenytoin 4-hydroxylase for CYP2C19, bufuralol 1-hydroxylase for CYP2D6, lauric acid 11-hydroxylase for CYP2E1, and testosterone 6β-hydroxylase for CYP3A4. Selective CYP450 inhibitors were used as positive controls. At concentrations up to 100 μM, lenalidomide did not inhibit CYPs 1A2, 2C9, 2C19, 2E1, or 3A4. CYP2D6 was initially inhibited in the presence of lenalidomide compared to the negative control; however, IC_{50} analysis indicated that lenalidomide did not significantly effect CYP2D6 activity.

Administration of lenalidomide to Sprague Dawley rats at dose levels of up to 300 mg/kg/day did not result in the induction of CYP1A, CYP2B, CYP2E, CYP3A, or CYP4A. Administration to male and female cynomolgus monkeys at dose levels of up to 2 mg/kg/day had no effects on hepatic, microsomal protein, or cytochrome P450 concentrations or on the activities of CYP1A, CYP2B, CYP2C, CYP2E, CYP3A, or CYP4A.

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

Studies of lenalidomide's ability to act as a substrate and/or an inhibitor of P-glycoprotein transport processes have not been performed.

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

Metabolic/transporter pathways for lenalidomide have not been studied.

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?

No, the indication is for monotherapy.

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

MDS patients frequently receive growth factors (personal communication: reviewing Medical Officer).

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. The only drug interaction study performed studied the effect of lenalidomide on the pharmacokinetics and activity (clotting time) of warfarin. The study included measurement of leanlidomide pharmacokinetics. Neither drug's pharmacokinetics were altered by co-administration.

2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

No pharmacodynamic drug-drug interactions have been described and there is no mechanistic basis to hypothesize that pharmacodynamic drug-drug interactions may occur.

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

Characterization of the metabolites formed following lenalidomide administration to humans has not been performed. As lenalidomide is structurally similar to the teratogen thalidomide, there is concern that lenalidomide could produce thalidomide-like teratogenicity. The package insert precludes administration to pregnant women and a special program, similar to the STEPS program for thalidomide, will be instituted to preclude mis-prescribing to pregnant women.

In order to investigate the chemical breakdown products of lenalidomide when compared to thalidomide, an assessment was performed to evaluate the theoretical in vivo metabolism of both products (Celgene Study No. 001, NDA Section 2.6.5.11). Three chemical reactions are involved in the chemical hydrolysis of thalidomide and lenalidomide including racemization via the loss of an acidic proton at the chiral carbon atom which includes reprotination of the keto-enol intermediate; hydrolysis of the imide bonds, and hydrolysis of the amides to carboxylic acids. The Applicant's analysis showed no common degradation pathways that would lead to common intermediates. There is no data to support that lenalidomide converts or breaks down into thalidomide. Therefore, the Applicant holds that the toxicological and biological properties of lenalidomide are separate and distinct from thalidomide.

2.4.2 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

Approximately 80% of patients in study MDS-003 had dose reductions during the study. As the activity of dose lower than 10 mg is unknown, it is possible that a lower dose could provide less toxicity while retaining efficacy. A study is currently under way in Europe, study MDS-004, that includes an arm where patients are dosed at 5 mg QD.

Lack of data on the ability of less toxic regimens to produce efficacy is an unresolved significant omission. This omission will be partially remedied by the study of a 5 mg dose in MDS-004.

2.5. General Biopharmaceutics

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

The Applicant classifies lenalidomide as BCS Class 3: High Solubility - Low Permeability.

Lenalidomide can be classified as a highly soluble compound. Lenalidomide has the highest solubility of) at pH 1.2 with the solubility greater than , in pH 4.6, 6.8 and 7.4.

Lenalidomide does not degrade in at over however, in lenalidomide does degrade over time. Over , no degradation products were detected at any pH. At , however, the degradation has been shown to range from in

In the non-GLP study 03-CELG-NJ.P01, the highly hydrophilic compound lenalidomide showed low permeability in the Caco-2 system, but high permeability in the PAMPA system. The difference between systems could be explained by the presence/absence of active transporters or differences in membrane structure. The Applicant classifies lenalidomide as a low permeable substance, being the more conservative category.

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

The three clinical studies (MDS-501-001, CC-5013-MDS-002 and CC-5013-MDS-003) used a 10-mg dose (two 5-mg capsules). The to-be-marketed formulation is a 10-mg capsule. A relative bioavailability study has not been performed. The NDA includes a request for a biowaiver.

The biowaiver request is based upon four criteria:
a) the 10-mg dose is clinically safe and efficacious,
b) linear pharmacokinetics occurs between 5-mg and 10-mg,
c) the composition of the 10 mg capsule is proportionally similar to the 5-mg capsule, and
d) the dissolution for the 10-mg strength capsule is similar to the 5-mg strength capsule.

Item "a)", the clinical safety and efficacy of a 10-mg dose, will be determined by the clinical division.

Item "b)" is that linear pharmacokinetics occurs between 5-mg and 10-mg. The Applicant shows the following data is support of this conclusion (**FDA Figure 6.** Applicant's

Figure 2 from Page 5 of *Biowaiver Request for a 10 mg Immediate Release Capsule of Lenalidomide*)

FDA Figure 6. Applicant's Figure 2 from page 5 of *Biowaiver Request for a 10 mg Immediate Release Capsule of Lenalidomide*

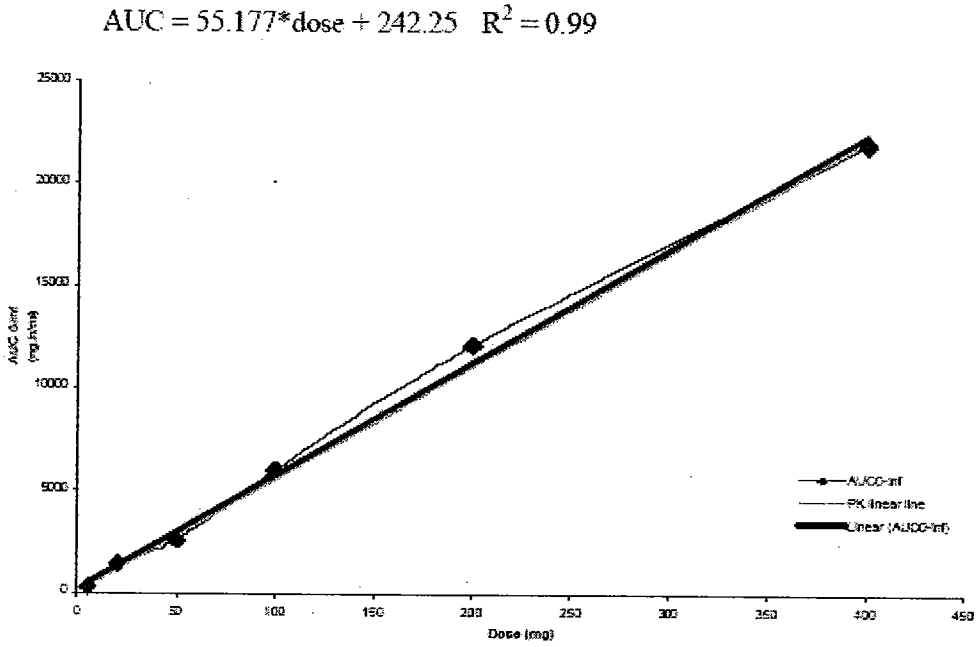
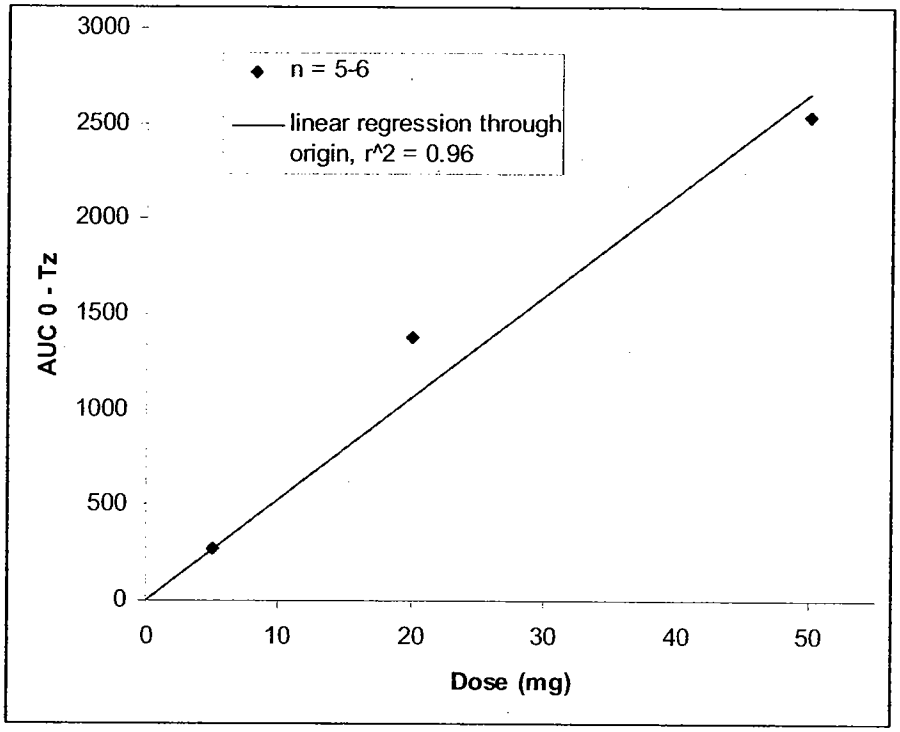


Figure 2 Pharmacokinetic linearity of lenalidomide.

The Reviewer used these same data (from Study 1398/142) in a slightly different way. To more specifically assess linearity within the range of interest (5 – 10 mg), and to avoid modeling assumptions, the Reviewer investigated the relationship between AUC measured and dose. AUC measured was, for all 16 patients, > 95% of AUC 0-inf. The results of the Reviewer's analysis are shown below (**FDA Figure 7.**)

FDA Figure 7. Dose-Linearity of Single Doses from 5 -50 mg



The Reviewer concludes that dose-linearity from 5 – 10 mg is established.

Item "c)" is that the composition of the 10 mg capsule is proportionally similar to the 5-mg capsule. The Applicant's Table 1 shows that the formulations are compositionally proportional. It is reproduced below as **FDA Table 9**.

FDA Table 9. Applicant's Table 1 from page 6 of *Biowaiver Request for a 10 mg Immediate Release Capsule of Lenalidomide*

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Table 1: Qualitative and Quantitative Composition of Lenalidomide Capsules, 5 mg and 10 mg

			5 mg Capsule	10 mg Capsule
Ingredient	**Quality Standard**	**Function**	**Theoretical Weight per Capsule (mg)**	
Lenalidomide[a]	In-house	Active	5.0	10.0
Lactose Anhydrous[b]	NF/EP			
Microcrystalline Cellulose (Avicel PH 102)	NF/EP			
Croscarmellose Sodium	NF/EP			
Magnesium Stearate	NF/EP			
Total Fill Weight	---	---	200.0	400.0
White Capsule Shells (Size 2) Imprinted with Black Ink[c]	In-house	---	1 Capsule	---
Pale Yellow Body/Blue Green Cap Capsule Shells (Size 0) Imprinted with Black Ink[c]	In-house	---	---	1 Capsule

[a]

[b]

[c] The capsule shells are supplied by — Information pertaining to the components and source of gelatin in the capsule shells is provided in 3.2.P.4.

Item "d)" is that the dissolution for the 10-mg strength capsule is similar to the 5-mg strength capsule.

The dissolution of the 5-mg and 10- mg capsules was evaluated for 12 dosage units of each in — in the following media: — Since the average % dissolved at 10 minutes was greater than — in all media for both the 5- and 10- mg capsules, an f_2 comparison was not performed.

In order to determine if the product would rapidly dissolve under less aggressive conditions, the — speed was changed to — for all media. The dissolution at 10 minutes was greater than — for both 5-mg and 10-mg in — Degradation correction of data and f_2 calculations were not performed for these two media given the rapid dissolution of both the 5- and 10-mg capsules. At 30 minutes, the percent dissolved was greater than — for all media. The f_2 at pH 4.5, 6.8 and 7.5 were 76, 59 and 60, respectively.

The proposed post-approval dissolution method for lenalidomide capsules, 5 mg and 10 mg, is . The proposed acceptance criterion is (Q) is dissolved in 30 minutes.

Based on these data, a biowaiver is granted for the 10-mg capsule.

2.5.3 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?

AUC_{0-tz} was not statistically different when 200 mg of lenalidomide was administered with food compared to when administered without food. However, C_{max} was decreased 36% under fed conditions.

The safety and efficacy trials (MDS-001 and MDS-003) were conducted without instructions on the timing of taking the drug relative to eating.

The Reviewer concludes that no recommendation regarding administration of the product in relation to meals or meal types is needed.

2.5.4 When would a fed BE study be appropriate and was one conducted?

Such a study would not be appropriate and was not conducted.

2.5.5 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

The dissolution method proposed for lenalidomide capsules, 5 mg and 10 mg, uses The proposed acceptance criterion is (Q) is dissolved in 30 minutes. In contrast to other conditions, these conditions provide discrimination between batches expected to show differences yet do not produce

Initial dissolution testing of lenalidomide capsules was performed in . results for all batches manufactured, were in the high range, usually within the first 10 to 20 minutes. Testing of a batch of lenalidomide capsules, 5 mg, (batch 0305W) produced with instead of ingredient, did not reveal any difference between the two batches.

Dissolution in other media at was then evaluated per the FDA Guidance for Industry.

All results are slower in than under the control conditions. Complete dissolution is not observed even after 45 minutes. Examination of individual capsule results shows a high degree of variability, with one batch, 0168W (not a clinical

batch), exhibiting unexpectedly low dissolution throughout its profile. Lab analysts reported that the capsules exhibited strange behavior in this medium, regardless of which batch was tested.

The Applicant concluded that was occurring and as such, would render this condition unsuitable for routine use. Investigation specifically into batch 0168W did not reveal any assignable cause for the variable dissolution results. This batch was manufactured more than one year before these studies were undertaken, as a result, additional sampling for more detailed analysis was not possible).

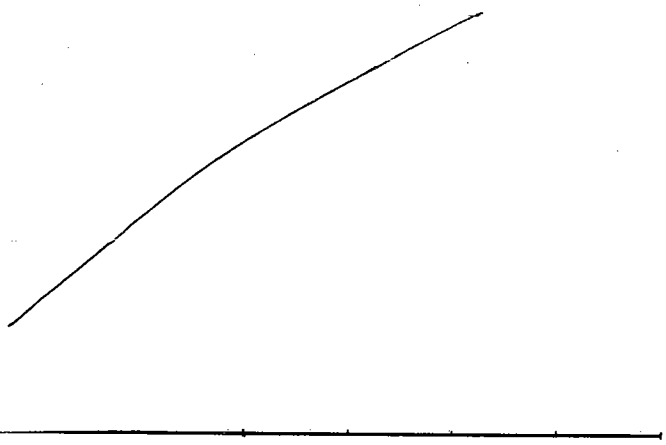
Results are uniformly slower and more variable in than under the control conditions. Complete dissolution was not observed even after 45 minutes. The behaviors seen in were not recorded by analysts studying conditions. However, concerns about the stability of lenalidomide had to be addressed (the drug substance is not stable /). Dissolution samples held for degraded between This long hold time was selected to determine the robustness of these conditions for routine quality control use. While a loss of does not impart a bias that is unreasonable in terms of the variability expected in typical dissolution studies, it has some potential to result in unnecessary Stage II testing with the associated investigations and documentation. For this reason, the Applicant did not select these conditions for further evaluation.

Since all three media recommended in FDA's guidance experienced deficiencies, a new medium was evaluated. Profiles comparing the registration batches in this medium vs. control were performed. Summary results are provided in **FDA Table 10**. There were no abnormalities from (lenalidomide is stable below

FDA Table 10. Applicant's Table 10 from page 10 of NDA Section 3.2.p.5.4 batch analysis

Table 10: Dissolution of Lenalidomide Capsules in

Batch	Data								
						,Control)			
		10 min	20 min	30 min	45 min	10 min	20 min	30 min	45 min
0379U (5mg)	Average								
	Range								
0035W (5mg)	Average								
	Range								
0168W (5mg)	Average								
	Range								
0226W (10mg)	Average								
	Range								
0227W (10mg)	Average								
	Range								
0228W (10mg)	Average								
	Range								



The final evaluation of this medium was its potential to discriminate between the and the batches. A comparative dissolution profile was performed in this medium. Summary data are shown in **FDA Table 11**.

FDA Table 11. Applicant's Table 11 from page 10 of NDA Section 3.2.p.5.4 batch analysis

Table 11: Dissolution of Lenalidomide Capsules, 5 mg Manufactured Using
vs.

Batch	Data								
						,Control)			
		10 min	20 min	30 min	45 min	10 min	20 min	30 min	45 min
0379U	Average								
	Range								
0305W	Average								
	Range								

is a condition where lenalidomide is soluble and stable, and discrimination between batches wherein a difference would be expected occurs. We conclude that post-marketing dissolution testing be performed using , sampling at 30 minutes with a Q=

2.5.6 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?

A waiver for the requirement for an in vivo demonstration of formulation similarity is granted. The basis for the waiver is described in section 2.5.2 of this review.

2.5.7 If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

The NDA is not for a modified release formulation of an approved immediate release product.

2.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either *in vitro* or in vivo data to evaluate BE?

Unapproved products or altered approved products were not used as active controls

2.5.9 What other significant, unresolved issues related to *in vitro* dissolution or in vivo BA and BE need to be addressed?

There are no other significant, unresolved issues related to *in vitro* dissolution or in vivo BA and BE.

2.5 Analytical section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Only lenalidomide was measured.

2.6.2 Which metabolites have been selected for analysis and why?

No metabolites were measured.

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 lenalidomide was measured. The extent of [^{14}C] CC-5013 binding in humans was 22.7% for patients with MM and 29.2% for healthy human volunteers.

2.6.4 What bioanalytical methods are used to assess concentrations?

2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

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

2.6.4.3 What are the accuracy, precision, and selectivity at these limits?

2.6.4.4 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

2.6.4.5 What is the QC sample plan?

1398/142: A Phase I, single-blind, placebo-controlled, ascending single oral dose, safety, tolerability and pharmacokinetic study in healthy male subjects incorporating a comparison of fed/fasted kinetics

The analytical method validated in report 1398/159 was used to determine the plasma concentrations of CC-5013 using — for sample preparation, followed by analysis using liquid chromatography with — spectrometric detection. — . The lower limit of quantification of CC-5013 in plasma was — ng/mL and the inter-assay precision of QC samples analyzed throughout the study was —

. The inter-assay accuracy varied between —

1398/180: A Phase I, single-blind, placebo-controlled, multiple oral dose, safety, tolerability, pharmacodynamic and pharmacokinetic study in healthy, male subjects

The analytical method validated in report 1398/159 was used to determine the plasma concentrations of CC-5013 using — for sample preparation, and liquid chromatography with — mass spectrometric detection. — The lower limit of quantification of CC-5013 in plasma was — ng/mL and the inter-assay precision of QC samples analyzed throughout the study was — over the range — ng/mL. The inter-assay accuracy varied between —

1398-271 (pharmacokinetic report for CDC-501-001): An Open Label Study of the Safety and Efficacy of CC-5013 Treatment for Patients with Relapsed Multiple Myeloma

A validated analytical procedure (1398/240) was used to determine CC-5013 in human plasma, using protein precipitation for sample preparation and liquid chromatography with — mass spectrometric detection — The lower limit of quantification (LLOQ) for CC-5013 in human plasma was — ng/mL, with linearity demonstrable to — ng/mL. The precision in the determination of the quality control samples was — at — The mean accuracy values at these levels were — , respectively.

CC-5013-PK-003: Healthy Volunteer Drug Interaction Study of Revlimid with Warfarin

The analytical method was developed and validated at , — Plasma samples containing EDTA are extracted using a — procedure. Calibration standards from — were used. Quality control samples of — — ng/mL were run in duplicate for both analytes (S-lenalidomide and R-lenalidomide). %CV was — , for all QC concentrations for both analytes across all 7 analytical runs. Stability was acceptable, including post-preparative stability which was tested up to — —

3 Detailed Labeling Recommendations

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7 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(5) Draft Labeling

4 Appendices

4.1 Package insert (proposed)

4.2 Cover sheet and OCPB filing/review form

Appendix 4.1 Package insert (proposed)

16 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Appendix 4.2 Cover sheet and OCPB filing/review form

I. *Office of Clinical Pharmacology and Biopharmaceutics*

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-880	Brand Name	Revilmid™
OCPB Division (I, II, III)	I	Generic Name	lenalidomide
Medical Division	Oncology	Drug Class	immunomodulator
OCPB Reviewer	Gene M. Williams, Ph.D.	Indication(s)	for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities
OCPB Team Leader	Brian Booth, Ph.D.	Dosage Form	5 and 10 mg oral capsules
		Dosing Regimen	10 mg QD w/dose reduction instructions in insert
Date of Submission	April 7, 2005	Route of Administration	oral
Estimated Due Date of OCPB Review		Sponsor	Celgene Corp.
PDUFA Due Date	October 2, 2005	Priority Classification	1P
Division Due Date	September 23, 2005		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:	x	1	1	
Blood/plasma ratio:				
Plasma protein binding:	x	1	1	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	1	1	
multiple dose:	x	1	1	
II. Patients-				
single dose:				
multiple dose:	x	1	1	
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:	x	1	1	
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				

geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	x	1		
In-Vitro Release BE	x	1		
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		4		

Filability and QBR comments		
	"X" if yes	Comments
Application filable?	x	
Comments sent to firm?		
QBR questions (key issues to be considered)	Biowaiver request – drug is BCS Class 3	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

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

/s/

Gene Williams
9/26/2005 11:39:01 AM
BIOPHARMACEUTICS

Brian Booth
9/26/2005 12:58:44 PM
BIOPHARMACEUTICS

Mehul Mehta
9/26/2005 05:10:34 PM
BIOPHARMACEUTICS