CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206088Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 206088 SUPPL # HFD # 540

Trade Name Otezla

Generic Name (apremilast)

Applicant Name Celgene Corporation

Approval Date, If Known: September 23, 2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(1)

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

YES ☒ NO ☐

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

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

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

5 years

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☒

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

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

1. Single active ingredient product.

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

YES ☒ NO ☐

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

NDA# 205437 Otezla (apremilast) tablets, 10, 20 and 30 mg

NDA#

NDA#

2. Combination product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical

investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

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

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

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

YES ☒ NO ☐

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

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

YES ☐ NO ☒

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

YES ☐ NO X☐

If yes, explain:

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

YES ☐ NO ☒

If yes, explain:

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

PSOR-008 and **PSOR-009 –** Randomized, Multicenter, Double-blind, Placebo-controlled, 52-Week Trial Evaluating the Safety and Efficacy of 30 mg Apremilast Tablet Administered Twice Daily for the Treatment of Adult Subjects with Moderate to Severe Psoriasis Who Were Candidates for Phototherapy or Systemic Therapy

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

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

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

Investigation #1 PSOR-008 YES ☐ NO ☒

Investigation #2 PSOR-009 YES ☐ NO ☒

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

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

Investigation #1 PSOR-008 YES ☐ NO ☒

Investigation #2 PSOR-009 YES ☐ NO ☒

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

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

PSOR-008 and **PSOR-009 –** Randomized, Multicenter, Double-blind, Placebo-controlled, 52-Week Trial Evaluating the Safety and Efficacy of 30 mg Apremilast Tablet Administered Twice Daily for the Treatment of Adult Subjects with Moderate to Severe Psoriasis Who Were Candidates for Phototherapy or Systemic Therapy

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

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

Investigation #1 PSOR-008 !

IND # 070270 YES ☒ ! NO ☐

! Explain:

Investigation #2 PSOR-009 !

IND # 070270 YES ☒ ! NO ☐

! Explain:

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

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

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

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

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Dawn Williams
Title: RPM
Date: 9/17/2014

Name of Division Director signing form: Tatiana Oussova
Title: Acting Director, DDDP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

DAWN WILLIAMS
09/23/2014

TATIANA OUSSOVA
09/23/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 206088 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Otezla Established/Proper Name: apremilast Dosage Form: tablets		Applicant: Celgene Corporation Agent for Applicant (if applicable):
RPM:		Division:

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is 9/23/2014	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☒ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Version: 5/14/2014

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approval Letter 9/23/2014
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	April 25, 2014 Proprietary Name Granted; April 22, 2014 Proprietary Name Review
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ None DMEPA: ☐ None April 11, 2014 DMPP/PLT (DRISK): ☒ None OPDP: ☐ None June 2, 2014 SEALD: ☒ None CSS: ☐ None Other: ☐ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC June 4, 2014 If PeRC review not necessary, explain: _____	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	March 24, 2014 Information Request; February 14, 2014 Information Request; January 28, 2014 Information Request; December 5, 2013 Filing Issues Identified; November 15, 2013 Acknowledge NDA
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	N/A
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg May 15, 2013
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg December 8, 2010 (Pre-Phase 3); March 12, 2010 (End of Phase 2)
• Mid-cycle Communication *(indicate date of mtg)*	☐ N/A May 7, 2014
• Late-cycle Meeting *(indicate date of mtg)*	☐ N/A June 3, 2014
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None September 23, 2014
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None September 19, 2014
PMR/PMC Development Templates *(indicate total number)*	☐ None 2
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	May 23, 2014
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☐ None

❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Page 14 of May 23, 2014 Clinical Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None June 2, 2014 Division of Cardiovascular and Renal Products; April 28, 2014 Division of Psychiatry Products
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☐ None June 16, 2014- No REMS recommended
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested July 16, 2014 Clinical Inspection Summary; August 20, 2014 VAI Foreign; August 18, 2014 NAI; June 5, 2014 NAI Foreign
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None May 9, 2014
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None May 5, 2014
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None April 1, 2014
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ No separate review
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None June 10, 2014 Product Quality; May 2, 2014 ONDQA/Biopharmaceutics
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed February 26, 2014
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	Page 23 of June 10, 2014 Product Quality review
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within **2 years** of action date) *(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[5])*	Date completed: June 9, 2014 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER (date of most recent TB-EER must be within **30 days** of action date) *(original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation

[5] i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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/s/

DAWN WILLIAMS
09/24/2014

PeRC PREA Subcommittee Meeting Minutes
June 4, 2014

PeRC Members Attending:
Gregory Reaman
George Greeley
Hari Cheryl Sachs
Andrew Mosholder
Robert “Skip” Nelson (b) (4)
Daiva Shetty
Gregory Reaman
Rosemary Addy
Wiley Chambers

PREA

10:50	NDA	206088	Otezla (apremilast) Partial Waiver/Deferral/Plan	Treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy

(b) (4)

Otezla Partial Waiver/Deferral/Plan

- NDA 206088 seeks review of Otzela (apremilast) for the treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy
- The applications have PDUFA goal dates of September 23, 2014.
- The application triggers PREA as a new indication.
- The Division clarified that the target PK is expected to be similar between adults and pediatric patients. However, they do not have any PK/PD (exposure-response) information to determine if extrapolation is possible. A PPSR was submitted by the sponsor for this moiety but was responded to with an Inadequate Letter.
- *PeRC Recommendations:*
  - The PeRC agreed with the Division to grant a partial waiver in patients ages birth to less than 6 years of age because studies are impossible or highly impractical and to the deferral in patients 6-17 years because the product is ready for approval in adults.
  - The PeRC recommends that the timelines for all studies be accelerated by 1 year.

(b) (4)


(b) (4)

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/s/

GEORGE E GREELEY
06/17/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206088

LATE CYCLE MEETING
BACKGROUND PACKAGE

Celgene Corporation
Attention: Gerlee D. Thomas
Associate Director, Regulatory Affairs
33 Technology Drive
Warren, NJ 07059

Dear Ms. Thomas:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Otezla (apremilast) tablets, 10, 20 and 30 mg.

We also refer to the Late-Cycle Meeting (LCM) scheduled for June 3, 2014. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Tatiana Oussova, MD, MPH
Deputy Director for Safety
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time:	June 3, 2014; 10:00am
Meeting Location:	Teleconference
Application Number:	NDA 206088
Product Name:	Otezla (apremilat) tablets, 10, 20 and 30 mg
Proposed Indication:	For the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy
Applicant Name:	Celgene Corporation

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

There are no substantive review issues at this time.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments – 5 minutes
   - Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Minor Review Issues – 2 minutes
   - Labeling discussions pending

3. Postmarketing Requirements/Postmarketing Commitments – 5 minutes
   - Post Marketing Requirement (PMR) for dose finding and pharmacokinetic/safety trials of (apremilast) tablets, 10, 20 and 30 mg in pediatric subjects age 6-17 years (b) (4) with moderate to severe plaque psoriasis

4. Review Plans – 5 minutes
   - At this time there are no significant review issues
   - The Office of Compliance inspection results for the manufacturing sites are pending
   - The Office of Scientific Investigation (OSI) inspection results are pending

5. Wrap-up and Action Items – 2 minutes

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/s/

TATIANA OUSSOVA
05/21/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 206088

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Celgene Corporation
33 Technology Drive
Warren, NJ 07059

ATTENTION: Gerlee D. Thomas
Associate Director, Regulatory Affairs

Dear Mr. Thomas:

Please refer to your New Drug Application (NDA) dated and received September 23, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Apremilast Tablets, 10 mg, 20 mg, and 30 mg.

We also refer to:

- Our email, dated February 07, 2014, requesting submission of your proprietary name under the NDA
- Our telephone conversation on February 11, 2014, confirming that although the proprietary name Otezla was previously submitted and approved for NDA 205437 in the Division of Pulmonary, Allergy and Rheumatology Products (DPARP), the same request for a proprietary name review should be submitted to DDDP for NDA 206088
- Your correspondence, dated and received February 21, 2014, requesting review of your proposed proprietary name, Otezla

We have completed our review of the proposed proprietary name, Otezla, and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your February 21, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Teena Thomas, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0549. For any other information regarding this application, contact Dawn Williams, Regulatory Project Manager in the Office of New Drugs, at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
04/25/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206088

MID-CYCLE COMMUNICATION

Celegene Corporation
Attention: Gerlee D. Thomas
Associate Director, Regulatory Affairs
33 Technology Drive
Warren, NJ 07059

Dear Ms. Thomas:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (apremilast) tablets, 10, 20, and 30 mg.

We also refer to the teleconference between representatives of your firm and the FDA on March 7, 2014. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Jill Lindstrom, MD
Cross Discipline Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time:	March 7, 2013; 9:30am
Application Number:	**NDA** 206088
Product Name:	(apremilast) tablets, 10, 20, and 30 mg
Proposed Indication:	For the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy
Applicant Name:	Celgene Corporation
Meeting Chair:	Jill Lindstrom, MD
Meeting Recorder:	Dawn Williams, BSN

FDA ATTENDEES
Jill Lindstrom, MD, Cross Discipline Team Leader, DDDP
Snezana Trajkovic, MD, Clinical Reviewer, DDDP
Dawn Williams, BSN, Regulatory Health Project Manager, DDDP
Mohamed Alosh, PhD, Biostatistics Team Leader, DB III
Matt Guerra, PhD, Biostatistics Reviewer, DB III

EASTERN RESEARCH GROUP ATTENDEES
Chelsea (So Hyun) Kim

APPLICANT ATTENDEES
Judith Abrams, MD, FRCPC, Executive Director, Clinical Research & Development
Jay Backstrom, MD, MPH, Senior Vice President, Global Regulatory Affairs & Pharmacovigilance
Khaled Bannout, MD, Senior Director, Lead Global Product Safety & Drug Safety/Risk Management
Lucy Chen, Director, Global Regulatory CMC
Gary Cline, PhD, Senior Director, Biostatistics & Programming
Wendy Corbet, Senior Director, Regulatory Affairs
Matthew Hoffman, PhD, Director, DMPK
Angela Hu, EdM, MS, Director, Biostatistics & Programming
Julia Hui, PhD, Senior Director, Toxicology
Philippe Martin, MS, MBA, Vice President, Global Project Leadership
Kristine Nograles, MD, Senior Director, Clinical Research & Development
Maria Paris, MD, Senior Director, Lead Global Product Safety & Drug Safety/Risk Management
Peter Schaefer, PhD, Director, Senior Principal Investigator, Translational Development
Gerlee Thomas, Associate Director, Regulatory Affairs
Dorothy Waddleton, Senior Director, Regulatory Affairs
Simon Zhou, Senior Director, Clinical Pharmacology

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

There are no significant issues identified at this time.

3.0 INFORMATION REQUESTS

There will be an information request forthcoming about adjudicated cases of MACE and potential MACE, and cases of depression.

Meeting Discussion:
The applicant noted that the cases of depression were not adjudicated. The Agency stated that we anticipate issuance of the information request regarding the above by the end of the week of March 10, 2014.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

There are no major safety concerns at this time, and no REMS is planned at this time.

5.0 ADVISORY COMMITTEE MEETING

There is not an advisory committee meeting planned at this time.

6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

The Agency is targeting the following date range for the Late-Cycle Meeting: May 27, 2014 through June 10, 2014.

Meeting Discussion:
The Agency anticipates initiation of labeling discussions by August 5, 2014 as noted in the Filing Communication.

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/s/

JILL A LINDSTROM
04/01/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206088

INFORMATION REQUEST

Celgene Corporation
Attention: Gerlee D. Thomas
Associate Director, Regulatory Affairs
33 Technology Drive
Warren, NJ 07059

Dear Ms. Thomas:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (apremilast) tablets, 10, 20 and 30 mg.

We are reviewing the clinical section of your submission and have the following comments and information requests. We request a prompt written response by April 4, 2014, in order to continue our evaluation of your NDA.

1. Provide (or indicate the location in the NDA of) a summary table and narratives for all adjudicated cases of MACE and potential MACE for the following trials: PSOR008, PSOR009 and PSOR 005.

2. Provide (or indicate the location in the NDA of) a summary table and narratives for all reported cases of depression, depressed mood, suicidal ideation, attempted suicide, and suicide for the following trials: PSOR008, PSOR009 and PSOR005.

3. You stated that you conducted an analysis to determine the relationship between the weight loss and gastrointestinal adverse events (ISS, section 5.4.2.5.3, page 187). Provide this analysis, or indicate its location in the NDA.

If you have any questions, please contact Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Jill Lindstrom, MD
Cross Discipline Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

DAVID L KETTL
03/24/2014

Thomas, Teena

From: Thomas, Teena
Sent: Friday, February 07, 2014 10:14 AM
To: 'gthomas@celgene.com'
Cc: Thomas, Teena; Anderson, Janet
Subject: NDA 206088 Proprietary Name submission

Hi Mr. Thomas,

The Division of Dermatology and dental Products(DDDP) is reviewing your NDA 206088 and came to know that you haven't submitted a proprietary name for this NDA. If you plan to submit the proprietary name for the NDA please submit as soon as possible. The proposed PDUFA date for this application is September 23, 2014.

Submit a new request for a proprietary name review that includes all required information as detailed in the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names,* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf.

Please feel free to contact me if you have any questions.

Thank you,

Teena

Teena Thomas, Pharm.D, CGP
Safety Regulatory Project Manager
FDA, CDER
Office of Surveillance and Epidemiology
Bldg.22, Room 3461
10903 New Hampshire Ave.
Silver Spring, Maryland 20993-0002

Tel: 301.796.0549
E-mail : teena.thomas@fda.hhs.gov

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/s/

TEENA THOMAS
02/14/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206088 **INFORMATION REQUEST**

Celgene Corporation
Attention: Gerlee D. Thomas
Associate Director, Regulatory Affairs
33 Technology Drive
Warren, NJ 07059

Dear Ms. Thomas:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (apremilast) tablets, 10 mg, 20 mg, and 30 mg.

We are reviewing the clinical section of your submission and have the following comments and information requests. We request a prompt written response by February 18, 2014, in order to continue our evaluation of your NDA.

For the following study population pool: Trials PSOR008, PSOR009, and PSOR005, provide the following analyses (or identify their location in the NDA):

1. Compare incidence of adverse events for:
   - Subjects randomized to apremilast 30mg two times per day dose for period Week 0 to Week 16.

   VS.
   - Subjects randomized to placebo for period Week 0 to Week 16

2. Compare incidence of adverse events for:
   - Subjects randomized to apremilast 30mg two times per day dose for period Week 0 to Week 52 (trials PSOR008 and PSOR009) and Week 0 to Week 48 for trial PSOR005.

   VS.
   - Subjects randomized to placebo for period Week 0 to Week 16 (PSOR008, PSOR009 and PSOR005).

Include tables presenting Adverse Events occurring in ≥1% of subjects for above listed analyses.

3. Compare incidence of Adverse Events of Special Interest (e.g. MACE; malignancies; systemic opportunistic infections):
   - Subjects randomized to apremilast 30mg two times per day dose for period Week 0 to Week 52 (trials PSOR008 and PSOR009) and Week 0 to Week 48 for trial PSOR005.

   VS.

- Subjects randomized to placebo for period Week 0 to Week 16 (PSOR008, PSOR009 and PSOR005). In addition, compare to external population as appropriate.

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Jill Lindstrom, MD
Clinical Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

JILL A LINDSTROM
01/28/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206088

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

Celgene Corporation
Attention: Gerlee D. Thomas
Associate Director, Regulatory Affairs
33 Technology Drive
Warren, NJ 07059

Dear Ms. Thomas:

Please refer to your New Drug Application (NDA) dated and received September 23, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for (apremilast) tablets, 10 mg, 20 mg and 30 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm . Therefore, the user fee goal date is September 23, 2014.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by August 5, 2014. In addition, the planned date for our internal mid-cycle review meeting is February 24, 2014. We are not currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issue:

Biostatistics

- Your current randomization and analysis does not allow for meaningful investigation of site-to-site variability. We recommended (Advice Letter 6/3/2011) designing the study so that centers enroll sufficient numbers of active and placebo subjects to adequately assess treatment effects within centers and treatment by center interactions. We also recommended using a randomization scheme that either stratified by center or allocate complete blocks to centers rather than using a study-wide randomization scheme. However, it appears that you did not implement our advice when conducting your randomization as your study centers showed substantial imbalance in treatment allocations.

We are providing the above comments to give you preliminary notice of a potential review issue. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to this issue during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

Chemistry, Manufacturing, and Controls

1. Clarify the discrepancy in bottle configurations between Table 16 in the Quality Overall Summary of NDA 206088 and Module 3.2.P.7 of NDA 205437, and Section 16 of the How Supplied of the Package Insert and Module 3.2.P.7.

Product Quality Microbiology

2. We acknowledge the microbial limits specification referenced test methods submitted in NDA 205437 (referenced by NDA 206088); however, results of methods suitability testing were not included. Provide verification of the methods of suitability for the finished drug product. Study summaries may be provided.

3. Drug product microbial limits acceptance criteria listed as "Complies with USP <1111> and Ph. Eur 5.1.4 requirements" in Table 14, Specifications for Apremilast Drug Product (Module 2.3 Introduction, page 27). Although both documents contain recommendations for microbial limits acceptance criteria, the drug product specification should be modified to include numerical limits for Total Aerobic Microbial Count and Total Yeasts and Molds Count, and also indicate testing for absence of specified microorganisms.

4. (b) (4)

(b) (4)

5. For the above product quality microbiology information requests, submit your responses to both NDAs 206088 and 205437.

Clinical Pharmacology

6. It appears that O-demethylated glucuronide metabolite (M-12) is the major metabolite and based on the results from trial CC-10004-CP-019, M12 exposure is 163% of the parent drug. Provide information on in-vitro evaluation of the (b) (4) responsible for the formation of M-12. In addition, provide information on the drug interaction potential of M-12. For further information, you are referred to the *Draft Guidance for Industry: Drug Interaction Studies- Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations (February 2012)*.

7. (b) (4)

8. Submit the datasets and codes/scripts for reviewers to evaluate population modeling and exposure-response analyses (especially for CC-10004-PSOR-005, CC-10004-PSOR-008, CC-10004-PSOR-009):

    a. All datasets used for model development and validation should be submitted as a SAS transport file (*.xpt). A description of each data item should be provided in a define.pdf file. Any data point and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. The flag of exclusion should be clearly explained in the define.pdf file.

    b. NONMEM model control streams and output listings for population PK and PK/PD report should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model (as found in Appendices). These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

    c. A dataset that includes one record per subject for your major exposure-response analyses. Major analysis codes and output listing for exposure-response report.

Biostatistics

9. For handling missing data, you used last observation carried forward (LOCF) as the primary method, with missing imputed as failure as sensitivity analysis. We previously recommended (End of Phase 2 meeting 5/12/2010; Advice Letter 6/3/2011) that you should include methods that use alternative assumptions as sensitivity analysis, e.g. multiple imputation or modeling approach. Provide the results using the recommended analysis methods.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult Division of Dermatology and Dental Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your request for a partial waiver of pediatric studies for children less than 6 years of age for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for children ages 6 to 17 years of age for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, MD, FAAD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

DAWN WILLIAMS
12/05/2013
Signing on behalf of Susan J. Walker, MD, FAAD, Director, DDDP

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206088

NDA ACKNOWLEDGMENT

Celgene Corporation
Attention: Gerlee D. Thomas
Associate Director, Regulatory Affairs
33 Technology Drive
Warren, NJ 07059

Dear Ms. Thomas:

We have received your New Drug Application (NDA) submitted under section 505(b)/pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: (apremilast) tablets, 10 mg, 20 mg, 30 mg

Date of Application: September 23, 2013

Date of Receipt: September 23, 2013

Our Reference Number: NDA 206088

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 22, 2013, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatology and Dental Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me, at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

CDR Dawn Williams, RN, BSN, USPHS
Regulatory Health Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

DAWN WILLIAMS
11/15/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 070270

MEETING MINUTES

Celegene Corporation
Attention: Gerlee Thomas
Senior Manager, Regulatory Affairs
33 Technology Drive
Warren, NJ 07059

Dear Ms. Thomas:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (apremilast) Tablets, 10 mg, 20 mg, and 30 mg.

We also refer to the teleconference between representatives of your firm and the FDA on May 15, 2013. The purpose of the meeting was to discuss the content and format of your proposed NDA submission.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Dawn Williams, Regulatory Project Manager at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, MD, FAAD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA Meeting
Meeting Date and Time:	May 15, 2013; 9:00 am
Meeting Location:	Teleconference
Application Number:	IND 070270
Product Name:	(apremilast) Tablets, 10 mg, 20 mg, and 30 mg
Indication:	Treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy
Sponsor Name:	Celegene Corporation
Meeting Chair:	Susan Walker, MD, FAAD
Meeting Recorder:	Dawn Williams, BSN

FDA ATTENDEES
Susan J Walker, MD, FAAD, Director, DDDP
David Kettl, MD, Clinical Team Leader, DDDP
Gary Chiang, MD, MPH, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Jianyong Wang, PhD, Pharmacology Reviewer, DDDP
Dawn Williams, BSN, Regulatory Health Project Manager, DDDP
Doanh Tran, PhD, Clinical Pharmacology Team Leader, DCP III
Mohamed Alosh, PhD, Biostatistics Team Leader, DB III
Kathleen Fritsch, PhD, Biostatistics Reviewer, DB III
Shulin Ding, PhD, Pharmaceutical Assessment Leader, DNDQA II
Doug Warfield, eData Team
Victoria Kusiak, MD, Deputy Director, ODE III

SPONSOR ATTENDEES
Judith Abrams, MD, Executive Director, Clinical Research & Development
Lucy Chen, Director, Global Regulatory CMC
Gary Cline, PhD, Senior Director, Statistics
Kara Hodes-Wechsler, RPh, Executive Director, Regulatory Affairs
Angela Hu, EdM, MS, Director, Biostatistics
Philippe Martin, MS, MBA, Executive Director, Global Project Leadership

Kamal Shah, MD, Executive Director, Global Drug Safety & Risk Management
Kathleen Steele, Associate Director, Medical Writing
Gerlee Thomas, Associate Director, Regulatory Affairs
Dorothy Waddleton, Senior Director, Regulatory Affairs

Regulatory Correspondence History
We have had the following meeting(s)/teleconference(s) with you:

- March 15, 2012, CMC Guidance
- December 8, 2010, Pre-Phase 3
- March 12, 2010, End of Phase 2
- December 10, 2007, Guidance
- July 27, 2005, Guidance
- August 27, 2004, Guidance
- August 25, 2004, Guidance

We have sent the following correspondences:
- November 1, 2012, Proposed Pediatric Study Request Inadequate
- October 3, 2012, Advice
- June 3, 2011, Advice
- April 12, 2011, Information Request
- April 6, 2011, IRB Waiver Granted
- March 31, 2011, Stability SPA
- January 14, 2010, Information Request
- November 9, 2009, Information Request
- September 24, 2009, Advice/Information Request
- September 22, 2008, Advice
- September 4, 2008, Advice
- August 6, 2008, Advice
- June 16, 2008, Advice
- May 21, 2008, Advice
- March 13, 2008, Advice
- March 1, 2007, Advice
- January 29, 2007, Advice
- October 3, 2006, Advice- Carcinogenicity SPA
- April 11, 2006, Advice
- March 2, 2006, Advice
- September 8, 2005, Advice
- August 24, 2004, Advice/Information Request

Regulatory
Question 1:

Based on the safety data and risk-benefit profile of apremilast presented within the briefing document, Celgene does not believe a REMS is needed to ensure benefits exceed potential risks and therefore is not planning on submitting a REMS as part of the NDA submission. Does the Agency agree with Celgene's proposal?

Response:
It is unlikely that a REMS will be required for the safe use of apremilast as a treatment of psoriasis based on our review of the summarized information contained in your meeting package. However, the final determination for necessity of a REMS depends on the overall risk benefit assessment of your application and will be decided after your complete application has been reviewed.

Question 2:
Celgene proposes to request 1) a waiver for pediatric subjects less than 6 years of age as psoriasis is less common in this age group than in older children and adolescents, and 2) a deferral for children and adolescents ages 6 through 17. Does the Agency agree with Celgene's proposal?

Response:
Your waiver request for subjects less than 6 years of age should be supported by sufficient rationale and information, including disease incidence and prevalence data related to pediatric plaque psoriasis, and an assessment of the feasibility of conducting trials in relevant pediatric populations. Note that Agency advice regarding a partial waiver at the March 12, 2010 EOP 2 meeting suggested an age limit at four years of age.

Your deferral request for older children through age 17 appears reasonable. However, you must submit a Pediatric Study Plan in accordance with PREA- see administrative comments below.

Question 3:
In this NDA submission and Agency filing, Celgene proposes to cross-reference the Chemistry, Manufacturing and Controls sections in Module 2.3 and Module 3, to the apremilast NDA submission for Psoriatic Arthritis (#205437) submitted on March 21, 2013 to the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP). Does the Agency agree with Celgene's proposal?

Response:
Yes, you may cross reference Modules 2.3 and Module 3 to NDA 205437. However, the following information will need to be provided in the proposed new NDA:

- Establishments
- Formulation composition table for the proposed to-be-marketed formulation
- Compositions of all clinical formulations, and a table correlating formulation, drug substance batch number, and drug product batch number with study numbers (clinical, toxicology, and stability).

- Drug substance specification table
- Drug product specification table
- List of DMFs with letters of authorization
- Description for each proposed packaging configurations
- Post approval stability commitment
- Proposed expiration dating period and storage condition
- A claim of categorical exclusion from the preparation of Environmental Assessment on the basis of 5 year combined production forecast for NDA 205437 and the proposed NDA.
- Any CMC changes since the submission of NDA 205437

Meeting Discussion:
The sponsor stated that there have been no CMC changes since submission of NDA 205347(psoriatic arthritis indication DPARP) and that the CMC information is identical between IND 070270 and NDA 205437. The Agency clarified that the CMC information requested above must be provided in the submission of the NDA for the psoriasis indication. The NDA submission must be complete.

Question 4:
As outlined in the guidance on *Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document*, Celgene proposes to split the ISE and the ISS between Module 2 and Module 5:

- The text portion of the ISE and ISS will be placed in Module 2 (Section 2.7.3 or 2.7.4, respectively), and the appendices and datasets will be placed in Module 5 (Section 5.3.5.3).
- Sections 2.7.3 and 2.7.4 will refer to Section 5.3.5.3 for the appendices and datasets.
- Section 5.3.5.3 will refer to Sections 2.7.3 and 2.7.4 for the text portion of the ISE and ISS.

Does the Agency agree with Celgene's proposal?

Response:
No the Agency does not agree. Situations where it may be appropriate to place the text portions of the ISE and ISS in Module 2 are rare, but can occur if the application is small and consists of a single study or a number of small studies. In general, Module 5 is the appropriate location for the ISE and ISS. This module is designed to contain more detailed in-depth analyses for the ISE and ISS.

Meeting Discussion:
The Agency clarified that the narrative text provided in Module 5 should be a complete analysis of the ISE and ISS.

Question 5:

Should DPARP hold an Advisory Committee on apremilast for the treatment of active psoriatic arthritis, is DDDP likely to hold an Advisory Committee on apremilast for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy?

Response:
The risk/benefit assessment of apremilast treatment for plaque psoriasis may be different than that of psoriatic arthritis and may warrant an Advisory Committee discussion.

Pharmacology/Toxicology

Question 6:
Celgene believes the nonclinical studies constitute a complete package that supports Agency filing and review of apremilast. Does the Agency agree?

Response:
Your nonclinical package appears acceptable to support a NDA submission. However, the final determination will be made after the review of all the final study reports submitted to the NDA.

Clinical Pharmacology/Biopharmaceutics

Question 7:
Celgene believes the clinical pharmacology studies constitute a complete package that supports Agency filing and review of apremilast. Does the Agency agree?

Response: The clinical pharmacology program appears reasonable to support filing. Adequacy of bridging among the different formulations used during development is a review issue.

Clinical/Biostatistics

Question 8:
Does the Agency agree that the efficacy data are sufficient for a NDA submission and Agency filing to review apremilast for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy?

Response:
The adequacy of your efficacy data is a review issue; however, we note that you have completed two phase 3 trials to support an NDA submission for the treatment of moderate to severe plaque-type psoriasis in subject who are candidates for phototherapy or systemic therapy.

Include the following items for your Phase 2 and Phase 3 studies in your submission:
1. The electronic datasets for clinical studies in SAS transport form (.xpt).

- You should submit both SDTM datasets (raw data directly from the CRF in standardized format) and analysis datasets. You might refer to the Analysis Data model (ADaM) Examples in Commonly Used Statistical Analysis Methods for guidance regarding analysis datasets: http://www.cdisc.org/stuff/contentmgr/files/0/5aee16f59e8d6bd2083dbb5c1639f224/misc/adam_examples_final.pdf.
- Each analysis dataset should include the treatment assignments, baseline assessments, and key demographic variables. The analysis datasets should include all variables needed for conducting all primary, secondary, and sensitivity analyses included in the study report. For endpoints that include imputations, both observed and imputed variables should be included and clearly identified.
- If any subjects were enrolled in more than one study, include a unique subject ID that permits subjects to be tracked across multiple studies.

2. Include dataset documentation (define.xml and define.pdf) for SDTM and analysis datasets. Definition files for raw datasets modeled according to CDISC/SDTM IG and standards should be submitted as .xml file types (define.xml). Refer to CDISC's Define.XML page for assistance/guidance related to creating define.xml files for CDISC/SDTM data. Also, for ease of viewing by the reviewer and printing, submit corresponding define.pdf files in addition to the define.xml. The analysis dataset documentation (define.pdf file) should include sufficient detail, such as definitions or descriptions of each variable in the data set, algorithms for derived variables (including source variables used), and descriptions for the codes used in factor variables.

3. Statistical programs for any non-standard analyses.

4. Study protocols including the statistical analysis plan, all protocol amendments (with dates), and an annotated copy of the Case Report Form (which maps variables in the datasets to the CRF).

5. The generated treatment assignment lists and the actual treatment allocations (along with date of enrollment) from the trials.

6. You are encouraged to arrange a test submission, prior to actual submission. Please refer to the Submit a Sample eCTD or Standardized Data Sample to the FDA Website (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm) for guidance on sending a test submission. You may request dataset(s) analysis for CDISC specifications compliance as part of the test submission. For additional information, contact the Electronic Submission Support Team at esub@fda.hhs.gov, or for standardized data submission questions, contact edata@fda.hhs.gov.

7. Refer to the CDER eCTD webpage for all current versions of specifications and guidances related to the eCTD:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm

8. Contact esub@fda.hhs.gov for any further questions related to preparing or submitting your eCTD submission.

Question 9:
Does the Agency agree that the proposed Statistical Analysis Plan (SAP) for the Integrated Summary of Efficacy (ISE) and two pivotal studies (CC-10004-PSOR-008 and CC-10004-PSOR-009) are sufficient for NDA submission and Agency filing?

Response:
The Pre-NDA meeting is not the appropriate venue for discussing SAPs for the individual studies as any discussions and agreements should be made at the protocol stage prior to the study, not after the studies have been completed and the study data have been analyzed. In general, SAPs should be based on the analyses specified in the protocol. We provided advice on protocols PSOR-008 and PSOR-009 on 6/3/2011. Ensure that your submission adequately addresses the issues from the letter such as assessment of site-to-site variability and sensitivity analyses.

Refer to the *Guidance for Industry: Integrated Summary of Effectiveness* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079803.pdf) for recommendations on what to include in the ISE. In particular, note that while pooled analyses of the Phase 3 studies can be a component of the ISE, the ISE should include discussions regarding the strength of evidence across all studies, including discussion of any difference in outcomes across studies.

Question 10:
Does the Agency agree that the safety data are sufficient for a NDA submission and Agency filing to review apremilast for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy?

Response:
The adequacy of the safety data is a review issue and is contingent upon the Agency review of the safety experience of your drug product. It appears that the safety experience of your product addresses the minimal requirements in terms of the numbers of exposed subjects and duration of exposure. We may have additional requests for safety information during the NDA review.

In addition to the information required in the ISS, provide shift tables for all laboratory values for both outside the normal range and outside the range that is considered clinically significant. Provide the normal range of values for all parameters, the threshold for concern for clinically significant change and your justification for why this threshold is appropriate.

As part of the safety assessments of your drug product, provide a complete evaluation of depression and suicidal behavior adverse events in all clinical trials with apremilast. Provide the incidence of depression, abnormal behavior, and suicidal ideations in all arms of your clinical trials. Address whether these events were prospectively addressed or are observations based on spontaneous reporting. The sponsor is referred to the draft Guidance for Industry: Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials.

Question 11:
Celgene is proposing to provide the following for unblended patients in the NDA submission for apremilast:

- Case Report Forms (CRFs) for deaths for (placebo and apremilast-treated patients), as well as all serious adverse events (SAEs) and all discontinuations due to adverse events (AEs) for pivotal and supportive studies (for apremilast-treated subjects only).
- Prose narratives for deaths (for placebo and apremilast-treated patients).
- Prose narratives for SAEs (for apremilast-treated patients only).
- Brief narratives with modified patient profiles for discontinuation due to AEs (for apremilast-treated patients only).

Does the Agency agree with Celgene's proposed plan?

Response:
The following data should be included:

- Subject narratives for all deaths, all serious adverse events (AEs), and AEs resulting in discontinuation from the trials conducted with your product.

- Case report forms (CRFs) for all serious AEs, all severe AEs, and for all subjects who discontinued from the studies for any reason. A study's CRFs should be placed in a CRF folder under the applicable study with a file tag of "case-report-forms." Also provide the following:

  Electronic links for:

  a. all serious AEs
  b. all severe AEs
  c. all patients discontinued regardless of reason
  d. all deaths

  CRFs should be referenced under the study in which it belongs and tagged as

  "case-report-forms" in that study's stf.xml file. CRFs that are not submitted should be readily available upon request.

- Adverse reaction tables (adverse reactions defined as those AEs with possible or probable causality) ≥ 1%.

- Adverse event tables ≥ 1% regardless of causality.

- Line listings for all safety data.

Meeting Discussion:
The Agency verified that CRF's for all discontinued subjects should be included in the NDA submission.

Question 12:
Celgene believes that the proposed SAP for the Integrated Summary of Safety/Summary of Clinical Safety (ISS/SCS), including the proposed safety tables are sufficient for a NDA submission and Agency filing. Does the Agency agree?

Response:
In general, the SAP for the ISS appears acceptable. See also the response to Question 11.

Administrative Comments

1. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21 CFR 54 and 21CFR 314.50(k).

2. We remind you of the Pediatric Research Equity Act of 2007 which requires all applications for a new active ingredient, new dosage form, new indication, new route of administration, or new dosing regimen to contain an assessment of the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations unless this requirement is waived or deferred.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry: Qualifying for Pediatric Exclusivity for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. We agreed that all data required to support approval of your NDA must be included with the NDA submission.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application

PREA REQUIREMENTS

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting occurred prior to November 6, 2012 or an EOP2 meeting will not occur, then:

- if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).
- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP, including a PSP Template, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm . In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57. In particular, please note the following formatting requirements:

- Each summarized statement in the Highlights (HL) must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.

- The section headings and subheadings (including title of the Boxed Warning) in the Table of Contents must match the headings and subheadings in the FPI.

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

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

I. Request for general study related information and specific Clinical Investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed Phase 3 clinical trials:

   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Current Location of Principle Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)

2. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 3 clinical trials:

   a. Number of subjects screened for each site by site
   b. Number of subjects randomized for each site by site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed Phase 3 clinical trials:

   a. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
   b. Name, address and contact information of all CROs used in the conduct of the clinical trials
   c. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
   d. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)

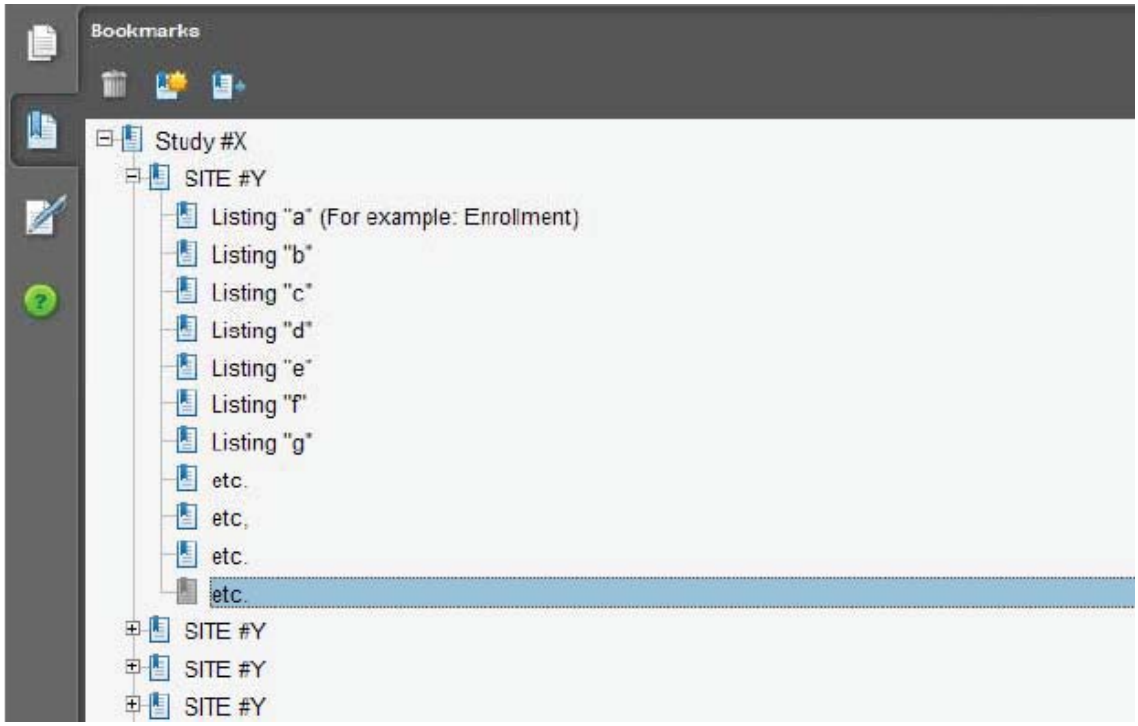
4. For each pivotal trial provide a sample annotated Case Report Form.
5. For each pivotal trial provide original protocol and all amendments.

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data ("line") listings. For each site provide line listings for:

a. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
b. Subject listing for treatment assignment (randomization)
c. Subject listing of drop-outs and subjects that discontinued with date and reason
d. Evaluable subjects/ non-evaluable subjects and reason not evaluable
e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
f. By subject listing, of AEs, SAEs, deaths and dates
g. By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of laboratory tests performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

DSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to the attached document, "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" for further information. We request that you provide a dataset, as outlined, that includes requested data for each pivotal study submitted in your application.

Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

I. I. INTRODUCTION

The purpose of this electronic submission of a single new clinical site dataset is to facilitate the timely evaluation of data integrity and selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

II. II. DESCRIPTION OF THE SUMMARY LEVEL CLINICAL SITE DATASET

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection and are not intended to support evaluation of efficacy. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

Site-Specific Efficacy Results

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- Treatment Efficacy Result Standard Deviation (TRTEFFS) – the standard deviation of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis
- Site-specific Efficacy Effect Size Standard Deviation (SITEEFFS) – the standard deviation of the site-specific efficacy effect size (SITEEFFE)
- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.
- Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) –the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, "TRTEFFR".

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.
- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.
- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).
- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the "endpoint" plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1.

III. III. CREATING AND SUBMITTING THE DATA FILE (SUBMISSION TEMPLATE AND STRUCTURE)

A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (*.xpt). The file may be submitted electronically through the FDA Electronic Submission Gateway (ESG) referencing the active IND number or via secure CD addressed to the Division of Scientific Investigations point of contact.

IV. Exhibit 1: Table 1 Clinical Site Data Elements Summary Listing (DE)

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter “1”.	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters).	Active (e.g., 25mg), Comparator drug product name (e.g., Drug x), or Placebo
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5
16	ENDPOINT	Endpoint	Char	String	Plain text label used to describe the primary endpoint as described in the Define file included with each application (limit 200 characters).	Average increase in blood pressure

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
18	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Efficacy result for each primary endpoint by treatment arm at a given site.	0, 0.25, 1, 100
19	TRTEFFS	Treatment Efficacy Result Standard Deviation	Num	Floating Point	Standard deviation of the efficacy result (TRTEFFR) for each primary endpoint by treatment arm at a given site.	0.065
20	SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	Site effect size with the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
21	SITEEFFS	Site-Specific Efficacy Effect Size Standard Deviation	Num	Floating Point	Standard deviation of the site-specific efficacy effect size (SITEEFFE).	0.065
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not applicable, enter -1.	5
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm. This value should include multiple events per subject and all event types (i.e., not limited to only those that are deemed related to study drug or treatment emergent events).	10
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by treatment arm. This value should include multiple events per subject.	5
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., not limited to only significant deviations).	20
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount ($USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	20000.00
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount ($USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parities. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	25000.00
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	MINITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

V. Exhibit 2: Example for Clinical Site Data Elements Summary Listing (Table 1)

STUDY	STUDYTL	DOMAIN	SPONNO	SPONNAME	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	ENROLL	SCREEN	DISCONT
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	27	60	1

VI.

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FINLDISC	LAST
Percent Responders	Binary	0.48	0.0096	0.34	0 0198	-1	0	2	0	1	-1	-1	
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	-1	
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	45000.00	Was
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45000.00	Was
Percent Responders	Binary	0.54	0.0092	0.35	0 0210	-1	2	2	0	1	15000.00	25000.00	Jef
Percent Responders	Binary	0.19	0.0059	0.35	0 0210	-1	3	6	0	0	22000.00	25000.00	Jef
Percent Responders	Binary	0.46	0.0095	0.34	0 0161	-1	4	1	0	0	0.00	0.00	Li
Percent Responders	Binary	0.12	0.0038	0.34	0 0161	-1	1	2	0	1	0.00	0.00	Li

MINITIAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

VII.

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

/s/

SUSAN J WALKER
06/13/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 070270

MEETING MINUTES

Celgene Corporation
Attention: Dorothy Waddleton
Director, Regulatory Affairs
86 Morris Avenue
Summit, NJ 07901

Dear Ms. Waddleton:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CC-10004 (apremilast) Capsules for the treatment of moderate to severe psoriasis in patients who are candidates for systemic therapy or phototherapy.

We also refer to the teleconference between representatives of your firm and the FDA on Wednesday, December 8, 2010. The purpose of the meeting was to discuss the development program for CC-10004.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Stanka Kukich, M.D.
Deputy Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

Official Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type A
Meeting Category:	Pre-Phase 3 Guidance Meeting
Meeting Date and Time:	December 8, 2010; 11:00 AM
Meeting Location:	Teleconference
Application Number:	070270
Product Name:	CC-10004 (apremilast) Capsules
Indication:	Treatment of moderate to severe plaque psoriasis in patients who are candidates for systemic therapy or phototherapy
Sponsor/Applicant Name:	Celgene Corporation
Meeting Chair:	Stanka Kukich, M.D., Deputy Director
Meeting Recorder:	Dawn Williams, B.S.N., Regulatory Project Manager

FDA ATTENDEES
Stanka Kukich, M.D., Deputy Director, DDDP
David Kettl, M.D., Clinical Team Leader, DDDP
Gary Chiang, M.D., Clinical Reviewer, DDDP
Barbara Hill, Ph.D., Pharmacology Supervisor, DDDP
Carmen Booker, Ph.D., Pharmacology Reviewer, DDDP
Shulin Ding, Ph.D., Pharmaceutical Assessment Leader, DNDQA II
Doanh Tran, Ph.D., Clinical Pharmacology Team Leader, DCP III
Abimbola Adebowale, Ph.D., Clinical Pharmacology Reviewer, DCP III
Lisa Mathis, M.D., Director, Pediatric and Maternal Health Staff
Jeannine Best, R.N., Senior Clinical Analyst, Pediatric and Maternal Health Staff
Dawn Williams, B.S.N., Regulatory Health Project Manager, DDDP

CELGENE ATTENDEES
Lucy Chen, Associate Director, Global Regulatory CMC
Gavin Corcoran, M.D., Executive Director, Clinical R&D, Inflammation and Immunology
Melanie Harrison, M.D., MSCE, Senior Director, Global Drug Safety and Risk Management
Julia Hui, Ph.D., Director, Toxicology
Philippe Martin, Executive Director, Global Project Leadership
Kamal Shah, M.D., Head of Trials Safety Surveillance

Meeting Minutes
Pre-Phase 3 Guidance Meeting
December 8, 2010

ODE 3/DDDP

Dorothy Waddleton, Director, Regulatory Affairs
Kara Hodes-Weschler, Senior Director, Regulatory Affairs
Anfan Wu, Senior Director, Exploratory Clinical Pharmacology

Regulatory Correspondence History

We have had the following meetings with you:
- End of Phase 2 Meeting- March 12, 2010
- Guidance Meeting- December 10, 2007

We have sent the following correspondences:
- Official meeting minutes, May 18, 2010
- Advice/Information Request, January 14, 2010
- Advice/Information Request, November 9, 2009
- Advice/Information Request, September 24, 2009
- Advice/Information Request, September 22, 2008
- Advice/Information Request, September 4, 2008
- Advice/Information Request, August 6, 2008
- Advice/Information Request, June 16, 2008
- Advice/Information Request, May 21, 2008
- Advice/Information Request, March 13, 2008
- Advice/Information Request, September 7, 2007
- Advice/Information Request, March 1, 2007
- Advice/Information Request, January 29, 2007
- Advice/Information Request, October 3, 2006
- Advice/Information Request, April 11, 2006
- Advice/Information Request, March 2, 2006
- Advice/Information Request, September 8, 2005
- Advice/Information Request, August 31, 2005
- Advice/Information Request, August 15, 2005
- Advice/Information Request, December 10, 2004 (2)
- Advice/Information Request, December 6, 2004 (2)
- Advice/Information Request, August 24, 2004

Chemistry, Manufacturing and Controls (CMC)

There were no specific CMC questions submitted. However, we have the following comment:

Color fading is reported for the commercial image tablets 20 mg and 30 mg in the annual report submitted on Oct. 26, 2010. Please address this stability issue and clarify which formulations are to be used in the proposed Phase 3 studies and whether the Phase 3 formulation will be identical to the to-be-marketed formulation.

Meeting Discussion:
The sponsor stated that they will be using the current commercial image tablet for their Phase 3 studies. They plan to update the stability data. They continue to see color fading under accelerated conditions. They believe the color fading is due to the (b) (4)

(b) (4). The color fading will be addressed in the future for the to-be-marketed product. The Agency responded that the Phase 3 formulation will not be identical to the to-be-marketed formulation if they plan to (b) (4) and additional bridging studies may be necessary depending upon the significance of the change. The Agency will not be able to assess the significance of the change until receiving the actual formulation composition information for Phase 3 and the to-be-marketed formulations. The sponsor responded that they plan to (b) (4) and the actual formulation information will be submitted to the NDA.

Pharmacology/Toxicology

There were no specific Pharmacology/Toxicology questions submitted; however, pharm/tox has the following comment.

While the Agency agrees that the NOAEL for the monkey embryofetal development study is 20 mg/kg/day, we do not agree with your statement that "there were no test-related malformations detected at any dose". Fetuses lost before cesarean section were not evaluated for malformations; therefore, it is impossible to know if teratogenicity was present in those fetuses.

Meeting Discussion:
The sponsor agreed with the Agency's assessment of monkey embryofetal development study report.

Clinical/Clinical Pharmacology/Biopharmaceutics

Background
Based on the available nonclinical and clinical data (which includes, in addition to the results of the completed cynomolgus monkey embryo-fetal study described here, nonclinical and clinical data previously reported in the End of Phase 2 Briefing Book submitted to the IND April 8, 2010, Sequence 0142), Celgene proposes the following pregnancy prevention measures be used in Phase 3.

Question 1:
Does the Agency agree with the proposed pregnancy prevention measures to be used in Phase 3 as outlined above?

Response:
The Agency recommended contraception measures for Apremilast Phase 3 clinical trials are as follows:

For Women of Childbearing Potential (WOCBP) enrolled in Apremilast clinical trials:

One highly effective contraception method, listed below:

- Intrauterine device (IUD)

- Hormonal (injections, implants, transdermal patch, vaginal ring)
- Tubal ligation
- Partner's vasectomy

OR

Oral Contraceptives with a barrier method listed below

OR

Two barrier forms of contraception listed below:

- Male or female condom
- Diaphragm with spermicide
- Cervical Cap with spermicide
- Contraceptive Sponge

The informed consent must include information regarding the potential for decreased efficacy of oral contraceptive pills with Apremilast use. Education regarding correct and consistent use of effective contraception is paramount to the success of pregnancy prevention.

Contraceptive requirements for males should be based on the amount of Apremilast detected in semen. If male contraception is required due to drug level detected in semen, then a condom is the appropriate male contraceptive method.

All pregnancies in Phase 3 trials should be followed to completion of pregnancy and outcomes reported to the IND.

There were no specific Clinical Pharmacology/Biopharmaceutics questions submitted. However, we have the following comment:

While we acknowledge that you have conducted some studies to evaluate the potential for your study drug to cause drug-drug interactions, it does not appear that you addressed potential drug interactions between your apremilast and hormonal contraceptives. Prior to recommending the use of hormonal contraceptives as effective contraceptive methods in your proposed Phase 3 clinical trials we recommend that you address the potential for drug interactions between your apremilast and hormonal contraceptives.

Meeting Discussion:
The sponsor proposed that for patients using oral contraceptive pills that a barrier method of birth control be added.
The sponsor agreed to conduct a drug interaction study with oral contraceptive pills prior to NDA submission. This report will be submitted with the NDA submission.

Background:
Based on the proposed pregnancy prevention measures in Phase 3, and the current nonclinical and clinical data, Celgene proposed that at the time of registration apremilast be classified as Pregnancy Category C as per 21 CFR 201.57, with product labeling consistent with that regulation. Celgene will consider a pregnancy registry for apremilast at the time of registration.

Question 2:
Does the Agency agree with Celgene's proposal for eventual product labeling as it pertains to pregnancy prevention as outlined above?

Response:
Conclusions regarding all the safety aspects of your product cannot be determined at this time. Decisions about potential product labeling will be determined at the time of NDA review.

Biostatistics

There were no specific Biostatistics questions submitted.

Additional Clinical Comments:

Inclusion/Exclusion criteria of the Phase 3 protocols should include lists of prohibited concomitant drug products, if any.

Additional Administrative Comments

- Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND might identify additional comments or information requests.

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

/s/

STANKA KUKICH
01/11/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 070270

MEETING MINUTES

Celgene Corporation
Attention: Dorothy Waddleton
Director, Regulatory Affairs
86 Morris Avenue
Summit, NJ 07901

Dear Ms. Waddleton:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for apremilast for the treatment of moderate to severe psoriasis who are candidates for systemic therapy or phototherapy.

We also refer to the meeting between representatives of your firm and the FDA on March 12, 2010. The purpose of this End of Phase 2 meeting was to discuss the development plan in adult patients with moderate to severe psoriasis who are candidates for systemic therapy or phototherapy.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, M.D., F.A.A.D.
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End of Phase 2 Meeting
Meeting Date and Time:	March 12, 2010, 10:00 AM
Meeting Location:	White Oak Campus, Building 22, Room 1311
Application Number:	IND 070270
Product Name:	apremilast
Indication:	treatment of moderate to severe psoriasis
Sponsor/Applicant Name:	Celgene Corporation
Meeting Chair:	Susan Walker, M.D.
Meeting Recorder:	Dawn Williams, B.S.N.

FDA ATTENDEES

Susan Walker, M.D., F.A.A.D., Director, DDDP
Stanka Kukich, M.D., Deputy Director, DDDP
David Kettl, M.D., Clinical Team Leader, DDDP
Gary Chiang, M.D., Clinical Reviewer, DDDP
Jane Liedtka, M.D., Clinical Reviewer, DDDP
Barbara Hill, Ph.D., Pharmacology Team Leader, DDDP
Carmen Booker, Ph.D., Pharmacology Reviewer, DDDP
Shulin Ding, Ph.D., Pharmaceutical Assessment Lead, DPA II Branch III
Dennis Bashaw, Pharm.D., Director, DCP III
Abimbola Adebowale, Ph.D., Clinical Pharmacology Reviewer, DCP III
Mohamed Alosh, Ph.D., Biostatistics Team Leader, DB III
Kathy Fritsch, Ph.D., Biostatistics Reviewer, DB III
Dawn Williams, B.S.N., Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Robert Day, Ph.D., Senior Director, Clinical Development
Kara Hodes-Wechsler, Senior Director, Regulatory Affairs
Angela Hu, Associate Director, Biostatistics and Statistical Programming
Julia Hui, Ph.D., Director, Toxicology
Michael Needle, M.D., Vice President, Pediatric Strategy
Peter Schafer, Ph.D., Director, Translational Development
Kamal Shah, M.D., Head of Trials Safety Surveillance
Victor Sloan, M.D., Vice President, Clinical Research, Inflammatory & Immunology
Wolf Ulrich-Nickel, Ph.D., Global Project Leader
Dorothy Waddleton, Director, Regulatory Affairs
Anfan Wu, Ph.D., Senior Director, Exploratory Clinical Pharmacology

Regulatory Correspondence History

We have had the following meetings with you:

- Guidance Meeting 12-10-2007

We have sent the following correspondences:

- Advice/Information Request 8-24-2004
- Advice/Information Request 12-6-2004 (2)
- Advice/Information Request 12-10-2004 (2)
- Advice/Information Request 8-15-2005
- Advice/Information Request 8-31-2005
- Advice/Information Request 9-8-2005
- Advice/Information Request 3-2-2006
- Advice/Information Request 4-11-2006
- Advice/Information Request 10-3-2006
- Advice/Information Request 1-29-2007
- Advice/Information Request 3-1-2007
- Advice/Information Request 9-7-2007
- Advice/Information Request 3-13-2008
- Advice/Information Request 5-21-2008
- Advice/Information Request 6-16-2008
- Advice/Information Request 8-6-2008
- Advice/Information Request 9-4-2008
- Advice/Information Request 9-22-2008
- Advice/Information Request 9-24-2009
- Advice/Information Request 11-9-2009
- Advice/Information Request 1-14-2010

Chemistry, Manufacturing and Controls (CMC)

There were no CMC questions identified in your briefing package.

Pharmacology/Toxicology

Question 1:
Does the Agency agree that the nonclinical studies completed to date are sufficient to support the conduct of the proposed phase 3 studies in moderate to severe plaque psoriasis?

Response:
Yes. The nonclinical studies completed and ongoing appear to be sufficient to support phase 3 studies. However, the final determination is a review issue. You must submit the monkey embryofetal development study report prior to initiation of phase 3 studies.

Meeting Discussion:

The sponsor stated that they will provide an audited draft study report for the oral monkey embryo-fetal development study in early June and plan to submit the phase 3 clinical study protocol in early August. The Agency responded that the audited draft study report would be acceptable if the study report contained complete data that would normally be contained in a complete study report (including individual animal data). The sponsor stated that audited draft study report would contain data from the initial three dose levels, but not from the additional low-dose added to determine a NOAEL for the embryo-fetal lethality. The Agency clarified that adequate number of fetuses would be needed for the doses evaluated for an adequate determination of teratogenicity.

The determination regarding the adequacy of the information for proceeding to phase 3 trials will be made after Agency review of the audited draft study report.

Question 2:
Does the Agency agree that the nonclinical program is sufficient to support registration of apremilast in the proposed indication?

Response:
Your nonclinical program appears acceptable to support submission of an NDA. However, the final determination is a review issue.

Question 3:
Does the Agency agree with Celgene's assessment that a nonclinical phototoxicity study is not warranted?

Response:
Yes. A nonclinical phototoxicity study is not needed.

Clinical Pharmacology/Biopharmaceutics

Question 4:
Does the Agency agree that the completed and planned clinical pharmacology studies are sufficient to support registration of apremilast in the proposed indication?

Response:
The clinical pharmacology studies that have been completed and proposed appear reasonable to support filing of the NDA application. However, the adequacy of these studies to support registration is a review issue. We note that the information provided in your meeting package did not specify the formulations used in each study. Be advised that, if the commercial formulation is significantly different from the formulations(s) used during development, bridging data may be needed, if the data obtained with the formulations used during development are intended to be used in support of product approval and labeling language.

We acknowledge the planned clinical pharmacology studies outlined in this briefing package. We recommend that you refer to our FDA guidance for industry for the hepatic impairment, renal impairment and food effect studies for additional guidance on the conduct of these studies. The FDA guidance website address is as follows: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances

Clinical/Biostatistics

Question 5:
Does the Agency agree that data from the two proposed phase 3 studies in psoriasis (CC-10004-PSOR-008 and CC-10004-PSOR-009) are sufficient to support registration in the treatment of adults with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy?

Response:
The proposed phase 3 program appears to be supportive of this indication. The adequacy of the data to support the proposed indication will be a review issue.

Question 6:
Does the Agency agree with the proposed dose of 30 mg BID to be used in the phase 3 studies?

Response:
Given the phase 2 experience for psoriasis described in the briefing document, your proposed dose is reasonable. However, doses above 30 mg BID were not evaluated so that it is unclear if the dose is optimized for safety and efficacy given the dose ranging results from phase 2 psoriasis trials.

The treatment estimates from your phase 2 trials are based on PASI 75 response, and are not based upon a composite endpoint of PGA and PASI 75 success, which is the endpoint recommended for phase 3 trials. This may affect the planning and proposed statistical analyses for your phase 3 program.

While you have conducted a dose-ranging study to investigate the short-term treatment of psoriasis, it does not appear that you have addressed the issue of maintenance therapy and whether the same dose and frequency used for the initial treatment is the most appropriate dose during the maintenance period.

Dose ranging should be conducted in a manner which investigates the induction/loading phase separately from the maintenance phase, as dosing for maintenance or re-treatment upon relapse may be different than that required for the initial treatment phase. In early development, you are encouraged to fully explore dose ranging in order to select a dose that maximizes safety and efficacy for the different treatment periods you propose. Dose ranging studies should investigate safety and efficacy and incorporate all elements of dose ranging such as dose (concentration), frequency, and duration of therapy. Adequate dose ranging explorations in phase 2 would allow determination of the formulation most

likely to succeed in phase 3 with optimal risk/benefit profile (safety outcomes). Informational needs would include the assessment of differences between maintenance of effect, and re-treatment upon relapse, as well as disease response for treatment free intervals as the natural course of psoriasis includes the potential for waxing and waning of symptoms.

Product toxicity is likely related to cumulative product exposure over time, and you should consider conducting clinical trials with elements of dosing decrements to determine how your product will be used for maintenance therapy or re-treatment upon relapse. In order to ensure the public health investigations should address duration of effect and various dose concentrations and frequencies to be used for treatment of this chronic disease. Clinical trial data should be provided to elucidate the effects of long-term immunosuppression on both safety and efficacy. You should provide information concerning the duration of clinical trial data that you believe should be provided prior to approval of your drug product.

Provide the Agency the current status of all phase 2 clinical studies for the indication of psoriasis for review.

Question 7:
Does the Agency agree with the design of the proposed phase 3 studies?

Response:
See above discussion.

Question 8:
Does the Agency agree that the primary endpoint (b) (4) in the proposed phase 3 studies support registration in the proposed indication?

Response:
No. The Agency recommends defining success in phase 3 psoriasis clinical trials on the PGA (b) (4) for assessing treatment effect, and recommends use of a composite endpoint based on both endpoints, that is, a treatment success to be defined as (i) success on the PGA (b) (4).

Subject enrollment in the trial should be consistent with moderate to severe psoriasis based on your composite endpoint and your subjects should be candidates for systemic therapy.

In regards to the PGA scale, the preference for a 5-point scale is based on the success criteria of achieving “clear” or “almost clear” combined with 2 point reduction on the scale. A 2-point reduction on a 5-point scale is more clinically meaningful than that on a 6-point scale.

The Division recommends defining the PGA scale based on description of the overall disease severity. This scale should have morphologic descriptor that clearly describe the

severity levels of the clear, almost clear, mild, moderate, and severe. You should clarify how the PGA score will be determined if the assessments for plaque elevation, scaling and erythema are discordant, especially at higher severity levels. Which descriptor will be weighted more heavily in this case?

Detailed comments for phase 3 protocols can be provided upon submission of the complete protocols.

The following are some general points regarding the statistical analysis as presented in the brief protocol concept sheets. Additional issues may arise when the full protocols are submitted.

The protocol concept sheets list a large number of secondary endpoints. The set of secondary endpoints intended to support efficacy should be clinically relevant and limited in number. The analysis of the secondary endpoints should adjust for multiplicity.

The protocol concept sheets state that the response variables will be analyzed with a chi-squared test. If the randomization is stratified by center, the Agency recommends analyzing the response rates with a Cochran-Mantel-Haenszel test stratified on center. Details of the randomization have not been included in the protocol concept sheets.

You have proposed to handle missing data with LOCF. In addition to the primary method of handling missing data, the protocols should include a few alternate methods of handling missing data as sensitivity analyses to ensure that the conclusions are not driven by the method of imputation. The sensitivity analyses should include methods that use alternate assumptions (e.g. multiple imputation, etc.).

You have proposed to conduct the studies in the U.S., Canada, and Europe. You should ensure that the design and conduct of the studies lead to results that are interpretable for and applicable to the U.S. population and include subgroup results by region.

Meeting Discussion:
There was a general discussion regarding endpoints. The Agency clarified that for any subject, success is considered to be demonstrated by achieving success on both PASI and PGA (clear or almost clear and at least two grades reduction from baseline).

Question 9:
Does the Agency agree that the proposed safety database will be sufficient to support registration in the proposed indication?

Response:
There appears to be adequate numbers of subjects in the safety database to support filing. The sufficiency of the information will be a review issue. The Agency considers psoriasis to be a chronic indication and therefore the duration of drug exposure and its relationship to both time and magnitude of occurrence of adverse events are important

considerations in determining the size of the database necessary to achieve an adequate safety data base. Additional safety data may be required if new safety signals are observed during the conduct of the Phase 3 clinical trials that require further characterization.

Safety information from all trials for Apremilast for various indications will be considered during the review process and should be submitted for review with the NDA. It is not clear at this time how the experience from rheumatoid arthritis, (b) (4) subjects will impact the risk benefit calculus for this non-life threatening indication of moderate to severe plaque psoriasis population.

We refer you to ICH-E1A Guideline for Industry, The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions.

Question 10:
Does the Agency agree with the proposed safety monitoring in the phase 3 program?

Response:
The safety monitoring plan which includes a Safety Review Panel seems to be appropriate for proceeding to the initial treatment phase of phase 3 clinical trials. Refer to Guidance for Clinical Trial Sponsors: Establishment of Operations of Clinical Trial Data Monitoring Committee for responsibilities and memberships of your Safety Review Panel.

Adequacy of safety monitoring for the maintenance phase (Weeks 16-32), the randomized withdrawal phase (Weeks 32-52), and the long-term extension phase (5 year duration) will depend on the 16 week safety data collected on psoriasis subjects as well as other ongoing studies.

Additional Comment:
As described in your briefing packet, in non-clinical toxicology studies and in clinical studies, exposure to apremilast was associated with a drug-induced inflammatory vasculopathy that resolved after discontinuation of the drug. We recommend that inflammatory biomarkers be continued in all phase 3 and future trials with this drug.

Meeting Discussion:
The sponsor will submit a discussion of the utility of assessing inflammatory biomarkers in their development program.

Question 11:
Does the Agency agree that the proposal to discontinue screening for latent TB in our phase 3 studies is appropriate?

Response:

Based on the current safety database, your phase 2 studies to date have included tuberculin screening and exclusion of subject with positive tests for latent TB. Your proposal to discontinue tuberculin screening yet retain chest radiography and brief review of systems to evaluate the presence of active TB at study entry is acceptable. However, occurrence of opportunistic mycobacterial infections during the phase 3 trials would necessitate re-evaluation of the proposed TB screening. Additionally, any screening procedure that is included in phase 3 clinical trials may be subject to inclusion under product labeling, should your drug product receive eventual approval for this indication.

Question 12:
Does the Agency agree with the proposed contraception and pregnancy monitoring in the phase 3 program?

Response:
The acceptability of your proposed contraception and pregnancy monitoring plans for your phase 3 protocols is contingent upon adequately addressing the non-clinical information requirements outlined above in our response to question 1. Based on the current information, two forms of contraception will be required for both male and female subjects. You should address how this requirement will impact eventual product labeling and the necessity of a Risk Evaluation and Mitigation Strategy should your product receive eventual approval for this indication.

A determination regarding proceeding to phase 3 trials for psoriasis will be made following complete characterization of the developmental and reproductive toxicities of your product. Clarify how your contraceptive requirements will impact the necessity of a Risk Evaluation and Mitigation Strategy (REMS) should your product receive eventual approval for this indication. You are referred to the Draft Guidance for Industry: Format and Content of Proposed Risk Evaluation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications, published in September 2009.

Question 13:
Does the Agency agree with the proposed pediatric plan as outlined, including all proposed waivers and deferrals?

Response:
The Agency may consider a deferral of pediatric studies according to section 505B(a)(3)(A)(ii) of the Act. However, the sponsor should submit a scientific rationale with the reason (s) for deferring the assessments, a description of the planned studies, and evidence that the studies will be conducted with due diligence and at the earliest possible time.

The Agency may consider a request for a partial waiver for the evaluation of pediatric psoriasis in pediatric subjects less than 4 years of age. The sponsor should submit a waiver request that includes evidence that the request meets the statutory reason(s) for waiver of pediatric assessment requirements.

Additional Administrative Comments

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND might identify additional comments or information requests.

2. Please refer to the Guidance for Industry: Special Protocol Assessment and submit final protocol(s) to the IND for FDA review as a **REQUEST FOR SPECIAL PROTOCOL ASSESSMENT** (SPA). Please clearly identify this submission as an SPA in bolded block letters at the top of your cover letter. Also, the cover letter should clearly state the type of protocol being submitted (i.e., clinical or carcinogenicity) and include a reference to this End-of-Phase 2 meeting. Ten desk copies (or alternatively, an electronic copy) of this SPA should be submitted directly to the project manager.

3. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).

4. We remind you of the Pediatric Research Equity Act of 2007 which requires all applications for a new active ingredient, new dosage form, new indication, new route of administration, or new dosing regimen to contain an assessment of the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations unless this requirement is waived or deferred.

5. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry: Qualifying for Pediatric Exclusivity for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

6. We remind you that effective June 30, 2006, all submissions must include content and format of prescribing information for human drug and biologic products based on the new Physicians Labeling Rule (see attached website http://www.fda.gov/cder/regulatory/physLabel/default.htm for additional details).

7. You are encouraged to request a Pre-NDA Meeting at the appropriate time.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-70270	GI-1	CELGENE CORP	CC-10004 CAPSULES

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

/s/

SUSAN J WALKER
05/18/2010