CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205437Orig1s000

CHEMISTRY REVIEW(S)

Otezla® (Apremilast) Tablets, 10, 20 & 30 mg

NDA 205437

Chemistry, Manufacturing, and Controls

Division Director's Summary Basis of Action

Applicant: Celgene Corp
33 Technology Drive
Warren, NJ 07059

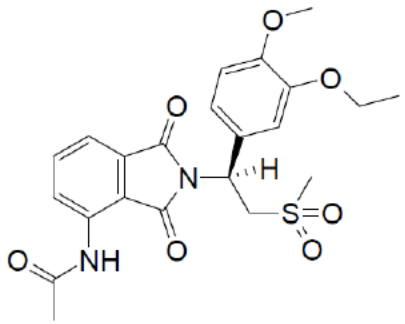
Indication: Apremilast drug product is intended to be used for the treatment of adult patients with active psoriatic arthritis. The recommended dose is a 30 mg tablet taken twice daily orally. Before the patient starts this regimen, a titration schedule is used. For day 1, a 10 mg tablet is used in the morning. Day 2, 10 mg is used in the morning and evening. Day 3, 10 mg in the morning and 20 mg in the evening. Day 4, 20 mg in the morning and evening. Day 5, 20 mg in the morning and 30 mg in the evening. Day 6 & after, 30 mg in the morning and evening.

Presentation: Apremilast will be packaged in bottles containing 60 tablets of 30 mg strength for regular use, and the 2-week starter pack is a blister pack containing 10 mg, 20, and 30 mg strengths of Apremilast.

EER Status:	Recommendations:	Acceptable - February 27, 2014.
Consults:	EA –	Categorical exclusion provided
	CDRH-	N/A
	Statistics –	Acceptable
	Methods Validation –	Acceptable
	DMETS-	Acceptable
	Biopharm–	Acceptable
	Microbiology –	Acceptable
	Pharm/toxicology –	Acceptable

Drug Substance:

The drug substance Apremilast is a white to pale yellow powder. The Biopharmaceutics Classification System places this compound in class 4 which is low solubility/low permeability. Apremilast is the S-enantiomer of N-[2-[1-(3-ethoxy-4-methoxy-phenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide. (b) (4) The structure of Apremilast includes an N-acylated aminoaryl function, which is a structural alert for potential mutagenicity. The drug substance is not photosensitive and the stability data provided supports both the proposed retest period of (b) (4), as well as the post-approval stability protocol.



IUPAC: N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide

Molecular Formula: $C_{22}H_{24}N_2O_7S$
Molecular Weight: 460.50 g/mol

The applicant has also followed Quality by Design (QbD) principles in their development of the manufacturing process for the drug substance and the method that will be used for the determination of drug substance assay and impurities. These approaches included the use of risk-based assessment to identify drug substance quality attributes and process parameters that had potential to impact drug product safety and efficacy. Critical quality attributes (CQAs) of the drug substance were identified and process parameters were categorized as critical or non-critical (CPPs or NCPPs). The applicant performed multivariate experiments and modeled output data to establish links between synthesis process parameters and the quality attributes of intermediates and the final drug substance. In this way they defined the acceptance criteria for the material attributes of the synthesis materials (starting materials, reagents, etc.) and process parameters, optimizing the process and providing greater assurance of the production of acceptable drug substance. In conjunction with these studies the applicant gained an understanding of the fate of and process parameters that affected the synthetic impurities in the drug substance. Overall, the applicant has presented additional information and data demonstrating enhanced process understanding of the drug substance synthesis process.

The final drug substance specifications include the following parameters: Appearance, Identity, Particle Size, Assay, Impurities, Residue on Ignition, Heavy Metals, Residual Solvents, and Chiral Purity.

The drug substance is manufactured at (b) (4) Celgene Chemicals GmbH - Switzerland. The drug substance is stored in (b) (4).

Drug Substance: Adequate.

Drug Product:

Apremilast is formulated as film-coated (b) (4) immediate release tablets available in three strengths, 10 mg, 20mg and 30 mg. The 10 mg tablets are pink, diamond shaped tablet with "APR" engraved on one side and "10" on the opposite side. The 20 mg tablets are brown, diamond shaped tablet with "APR" engraved on one side and "20" on the opposite side. The 30 mg tablets are beige, diamond shaped tablet with "APR" engraved on one side and "30" on the opposite side.

The tablets are manufactured with (b) (4) utilizing conventional excipients. Risk assessment and quality by design (QbD) approaches have been utilized for formulation and manufacturing process development. Comprehensive pharmaceutical development information is provided in the submission. Design space for the process parameters has been established through risk assessment, design of experiments, prior knowledge and modeling. However, this QbD approach is just for academic purposes. The sponsor will use this information to understand their manufacturing process.

The final drug product specifications include the following parameters: Appearance, Identity, Assay, Uniformity of Dosage Units, Degradation Products, Dissolution, and Microbial testing.

The drug product is packed in high-density polyethylene (HDPE) bottles or in (b) (4) blisters with push through foil.

The Drug Product is manufactured and packaged in Celgene International Sarl - Switzerland, (b) (4)

The submitted drug product stability data include 12 months at the long term storage condition of 30°C/65%RH and 6 month at the accelerated storage condition of 40°C/75%RH for 3 batches of each strength. The stability data support the proposed (b) (4) shelf life for the drug product when stored at the proposed 30°C or below.

However, a post market commitment was made for the final dissolution method. The final acceptance criteria and validation data will be sent to the FDA within 6 months of the action letter date. Therefore, in the action letter we propose an 18-month expiry dating period at 30°C or below for the Apremilast drug product.

Package Insert/Container and Carton labels

An updated package insert and container/carton labels were received on 02/27/2014 and 03/04/2014, respectively. The sponsor provides the container labels for the 30 mg blister pack, 30 mg starter pack and the carton container for the 30 mg blister pack and 30 mg starter pack. The label and carton provides the trade name, established name, strength of the active ingredient apremilast, expiration date period, Rx only statement, storage conditions, NDC number, bar code and the name of the manufacturer. The package insert and the container/carton labels are adequate from a CMC perspective.

Drug Product: Adequate. A Question Based Review pilot was conducted for the drug product section of this review.

Overall Conclusion:
From a CMC perspective, the application is recommended for approval.

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/s/

ERIC P DUFFY
03/10/2014

NDA 205437

Apremilast Film-Coated Tablets, 10, 20 &30 mg

Celgene

ONDQA/DNDQA III/Branch VIII, DNDQA II/Branch IV, and DNDQA I/Branch I
for
Division of Pulmonary, Allergy, and Rheumatology Products

REVIEW # 3
DATE: 05-MAR-2014

TO: N205437 File

FROM: Ciby J. Abraham, Ph.D.
Chemistry Reviewer
ONDQA, Division III, Branch VIII

THROUGH: Prasad Peri, Ph.D.
Acting Branch Chief
ONDQA, Division III, Branch VIII

SUBJECT: ACCEPTABLE recommendation from the Office of Compliance for NDA205437 on 27-Feb-2014.

ACCEPTABLE recommendation for document numbers 13 & 28 Labeling/Container-Carton Draft amendment on 02-OCT-2013 and 03-MAR-2014.

SUMMARY: The Office of Compliance has placed an overall recommendation of ACCEPTABLE into the EES on 27-FEB-2014. The Labeling/Container-Carton Draft amendment received on 2-OCT-2013 was evaluated and can be found in the primary review uploaded to DARRTS on 14-JAN-2014. The Labeling/Container-Carton draft amendment received on 03-MAR-2014 was found acceptable. CMC recommends the application for approval.

RECOMMENDATION: The application is recommended for **approval**.

_____
Ciby J. Abraham, Ph.D.
CMC Reviewer, ONDQA

OC Recommendation for NDA 205437

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 205437/000	**Sponsor:**	CELGENE
Org. Code:	570		86 MORRIS AVE
Priority:	1		SUMMIT, NJ 07901
Stamp Date:	21-MAR-2013	**Brand Name:**	APREMILAST TABLETS
PDUFA Date:	21-MAR-2014	**Estab. Name:**	
Action Goal:		**Generic Name:**	APREMILAST TABLETS
District Goal:	21-OCT-2013	**Product Number; Dosage Form; Ingredient; Strengths**	003; TABLET, FILM COATED; APREMILAST; 30MG 002; TABLET, FILM COATED; APREMILAST; 20MG 001; TABLET, FILM COATED; APREMILAST; 10MG

FDA Contacts:	C. ABRAHAM	Prod Qual Reviewer		3017960612
	N. SWEENEY	Micro Reviewer	(HFD-805)	2404023793
	Y. LIU	Product Quality PM		3017961926
	M. JORDAN GARNER	Regulatory Project Mgr	(HFD-570)	3017964786
	C. BERTHA	Team Leader		3017961646

Overall Recommendation:	ACCEPTABLE	on 27-FEB-2014	by J. WILLIAMS	()	3017964196
	PENDING	on 23-DEC-2013	by EES_PROD		
	PENDING	on 23-DEC-2013	by EES_PROD		
	PENDING	on 10-APR-2013	by EES_PROD		
	PENDING	on 10-APR-2013	by EES_PROD		
	PENDING	on 10-APR-2013	by EES_PROD		

Establishment:	**CFN:**	**FEI:**	3006305265
	CELGENE CHEMICALS GMBH UNTERE BRUHLSTRASSE 4 ZOFINGEN, , SWITZERLAND		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	03-JUN-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:**	**FEI:** 3006323509	
	CELGENE INTERNATIONAL SARL ROUTE DE PERREUX 1 BOUDRY, , SWITZERLAND		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE RELEASE TESTER DRUG SUBSTANCE STABILITY TESTER FINISHED DOSAGE MANUFACTURER FINISHED DOSAGE PACKAGER FINISHED DOSAGE RELEASE TESTER FINISHED DOSAGE STABILITY TESTER		
Profile:	TABLETS, PROMPT RELEASE	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	27-DEC-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:** (b) (4) (b) (4)	**FEI:** (b) (4)	
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER DRUG SUBSTANCE RELEASE TESTER DRUG SUBSTANCE STABILITY TESTER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	12-JUL-2013		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 29-APR-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 18-NOV-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 27-DEC-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

	(b) (4) (b) (4) (b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE MANUFACTURER FINISHED DOSAGE PACKAGER FINISHED DOSAGE RELEASE TESTER FINISHED DOSAGE STABILITY TESTER		
Profile:	TABLETS, PROMPT RELEASE	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	06-AUG-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:**	(b) (4)	**FEI:**	(b) (4)	
	(b) (4)				
DMF No:			**AADA:**		
Responsibilities:	FINISHED DOSAGE PACKAGER				
Profile:	TABLETS, PROMPT RELEASE		**OAI Status:**		NONE
Last Milestone:	OC RECOMMENDATION				
Milestone Date:	16-APR-2013				
Decision:	ACCEPTABLE				
Reason:	BASED ON PROFILE				

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
	DRUG SUBSTANCE RELEASE TESTER		
	DRUG SUBSTANCE STABILITY TESTER		
	FINISHED DOSAGE STABILITY TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	23-DEC-2013		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	27-FEB-2014		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:**	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	INTERMEDIATE MANUFACTURER		
	INTERMEDIATE RELEASE TESTER		
Profile:	API NON-STERILE (b) (4)	**OAI Status:**	NONE
	(b) (4)		
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	28-JAN-2014		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Labeling/Container-Carton draft amendment for 30 mg starter pack received on 03-MAR-2014

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/s/

CIBY J ABRAHAM
03/05/2014

PRASAD PERI
03/05/2014
I concur

CHEMISTRY REVIEW

NDA 205437

Apremilast Film-Coated Tablets, 10, 20 &30 mg

Celgene

Ciby J. Abraham, Ph.D.

ONDQA/DNDQA III/Branch VIII, DNDQA II/Branch IV, and DNDQA I/Branch I
for
Division of Pulmonary, Allergy, and Rheumatology Products

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A. Recommendation and Conclusion on Approvability 8

This drug product is recommended for approval from Chemistry, Manufacturing, and Control (CMC) perspective pending overall acceptable recommendation from the Office of Compliance. 8

The (b) (4) shelf life for the drug product when stored at (b) (4) is proposed and granted. ..... **Error! Bookmark not defined.**

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 8

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S.2 Manufacture [Apremilast, Celgene] 13

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Chemistry Review Data Sheet

1. NDA 205437

2. REVIEW #: 2

3. REVIEW DATE: 10-Jan-2014

4. REVIEWERS: Ciby J. Abraham, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	03/21/2013

7. NAME & ADDRESS OF APPLICANT:

Name:	Celgene Corp
Address:	33 Technology Drive Warren, NJ 07059
Representative:	Casilda Luck-Barnes, PharmD, Associate Director, Regulatory Affairs
Telephone:	(732) 652-6506

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Otezla
b) Non-Proprietary Name (USAN):
c) Code Name/# (ONDQA only): CC-10004
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Phosphodiesterase 4 (PDE4) inhibitor

11. DOSAGE FORM: Film-coated tablets

12. STRENGTH/POTENCY: 10, 20 & 30 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: ___X___Rx ___OTC

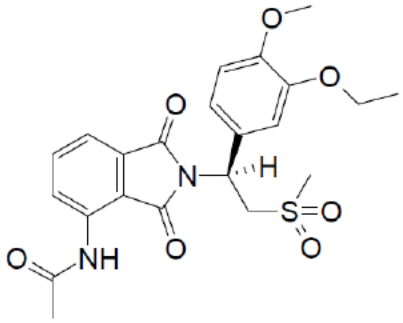
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

IUPAC: N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide

Molecular Formula: $C_{22}H_{24}N_2O_7S$
Molecular Weight: 460.50 g/mol



17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	III	(b) (4)		4	Adequate	N/A – MAPP 5015.5, Rev. 1	None

(b) (4)	III	(b) (4)	4	Adequate	N/A – MAPP 5015.5, Rev. 1	None
	III		4	Adequate	N/A – MAPP 5015.5, Rev. 1	None
	III		4	Adequate	N/A – MAPP 5015.5, Rev. 1	None
	III		4	Adequate	N/A – MAPP 5015.5, Rev. 1	None
	III		4	Adequate	N/A – MAPP 5015.5, Rev. 1	None
	III		4	Adequate	N/A – MAPP 5015.5, Rev. 1	None
	III		4	Adequate	N/A – MAPP 5015.5, Rev. 1	None
	II		4	Adequate	7/12/2013	The DMF has been reviewed.
	III		4	Adequate	N/A – MAPP 5015.5, Rev. 1	None

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There are enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

N/A

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	(b) (4)	Celgene	(b) (4)
IND	101761	Celgene	Apremilast (CC-10004) for treatment of (b) (4)

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	RECOMMENDATION	Date	Reviewer/Comment
Biometrics		3/26/13	Robert Abugov
EES	Pending	3/27/13	Waiting for inspection report
Pharm/Tox	approval	3/27/13	Lawrence Leshin
Biopharm	Pending	4/26/13	Minerva Hughes

Chemistry Review Data Sheet

Methods Validation	Pending	10/4/13	Michael Trehy
Microbiology	Pending	11/4/13	Neal Sweeney

The Chemistry Review for NDA 205437

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This drug product is approvable from Chemistry, Manufacturing, and Control (CMC) perspective pending overall acceptable recommendation from the Office of Compliance.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

A post market commitment was made for the final dissolution method. The final acceptance criteria and validation data will be sent to the FDA within 6 months of the action letter date.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance Apremilast is a white to pale yellow powder. The Biopharmaceutics Classification System places this compound in class 4 which is low solubility/low permeability. The proposed commercial drug product, apremilast tablets, contains 10 mg, 20 mg, and 30 mg apremilast and standard compendial excipients. The drug product will be packaged as bottles containing 60 tablets of 30 mg strength for regular use, and as a blister pack containing 10 mg, 20, and 30 mg strengths as a 2-week starter pack. The drug product (immediate-release tablets) is manufactured with (b) (4) The drug substance apremilast is (b) (4) by Celgene Chemicals in Zofingen, Switzerland. The drug product is manufactured and packaged at Celgene International Sarl facility in Boudry, Switzerland (b) (4) The drug product can also be packaged at (b) (4) All manufacturing and testing facilities associated with this application have acceptable inspection status. The various DMFs associated with the manufacture of the product are adequate or do not require review due to adequate information in the NDA. An expiry of 18 months is proposed and supported by submitted data. The storage condition storage conditions is 30 °C or below.

B. Description of How the Drug Product is Intended to be Used

Apremilast drug product is intended to be used for the treatment of adult patients with active psoriatic arthritis. The recommended dose is a 30 mg tablet taken twice daily orally. Before the patient starts this regimen, a titration schedule is used. For day 1, a 10

mg tablet is used in the morning. Day 2, 10 mg is used in the morning and evening. Day 3, 10 mg in the morning and 20 mg in the evening. Day 4, 20 mg in the morning and evening. Day 5, 20 mg in the morning and 30 mg in the evening. Day 6 & after, 30 mg in the morning and evening.

C. Basis for Approvability or Not-Approval Recommendation

The application is currently recommended as approvable pending comments from the Office of Compliance. The sponsor has provided adequate information in the manufacturing for the drug substance and drug product.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Ciby J. Abraham, Ph.D., CMC Reviewer
Prasad Peri, Ph.D., Branch Chief

C. CC Block

ODEII/DPARP/BChowdhury
OB/DBII/RAbugov
ODEII/DPARP/KHull
OCP/DCPII/SAgarwal
OPDP/DPP/PRG3/AAdeleye
OMP/DDMAC/OSalis
ODEII/DPARP/LLeshin
OSEIO/RAS/NRashid
OGD/OGDIO/NSweeney
ONDQA/YLiu
ODEII/DPARP/MGarner
ODEII/DPARP/SSeymour
ONDQA/Biopharm/MHughes
ONDQA/DNDQA3/CBertha

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/s/

CIBY J ABRAHAM
01/10/2014

PRASAD PERI
01/14/2014
I concur

CHEMISTRY REVIEW

NDA 205437

Apremilast Film-Coated Tablets, 10, 20 &30 mg

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The (b) (4) shelf life for the drug product when stored (b) (4) is proposed and granted. ..... **Error! Bookmark not defined.**

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 8

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S.7 Stability 97

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Chemistry Review Data Sheet

1. NDA 205437

2. REVIEW #: 1

3. REVIEW DATE: 20-Nov-2013

4. REVIEWERS: Ciby J. Abraham, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	03/21/2013

7. NAME & ADDRESS OF APPLICANT:

Name:	Celgene Corp
Address:	33 Technology Drive Warren, NJ 07059
Representative:	Casilda Luck-Barnes, PharmD, Associate Director, Regulatory Affairs
Telephone:	(732) 652-6506

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Otezla
b) Non-Proprietary Name (USAN):
c) Code Name/# (ONDQA only): CC-10004
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Phosphodiesterase 4 (PDE4) inhibitor

11. DOSAGE FORM: Film-coated tablets

12. STRENGTH/POTENCY: 10, 20 & 30 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: ___X___Rx ___OTC

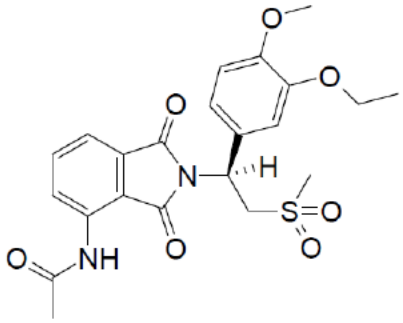
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

IUPAC: N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide

Molecular Formula: $C_{22}H_{24}N_2O_7S$
Molecular Weight: 460.50 g/mol



17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	III		(b) (4)	4	Adequate	N/A – MAPP 5015.5, Rev. 1	None

(b) (4)	III	(b) (4)	4	Adequate	N/A – MAPP 5015.5, Rev. 1	None
	III		4	Adequate	N/A – MAPP 5015.5, Rev. 1	None
	III		4	Adequate	N/A – MAPP 5015.5, Rev. 1	None
	III		4	Adequate	N/A – MAPP 5015.5, Rev. 1	None
	III		4	Adequate	N/A – MAPP 5015.5, Rev. 1	None
	III		4	Adequate	N/A – MAPP 5015.5, Rev. 1	None
	III		4	Adequate	N/A – MAPP 5015.5, Rev. 1	None
	II		4	Adequate	7/12/2013	The DMF has been reviewed.
	III		4	Adequate	N/A – MAPP 5015.5, Rev. 1	None

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There are enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

N/A

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	(b) (4)	Celgene	(b) (4)
IND	101761	Celgene	Apremilast (CC-10004) for treatment of (b) (4)

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	RECOMMENDATION	Date	Reviewer/Comment
Biometrics		3/26/13	Robert Abugov
EES	Pending	3/27/13	Waiting for inspection report
Pharm/Tox	approval	3/27/13	Lawrence Leshin
Biopharm	Pending	4/26/13	Minerva Hughes

Chemistry Review Data Sheet

Methods Validation	Pending	10/4/13	Michael Trehy
Microbiology	Pending	11/4/13	Neal Sweeney

The Chemistry Review for NDA 205437

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This drug product is recommended for approval from Chemistry, Manufacturing, and Control (CMC) perspective pending overall acceptable recommendation from the Office of Compliance, microbiology, biopharmaceutics and resolution of CMC IR comments sent to the sponsor.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

A post market commitment was made for the final dissolution method. The final acceptance criteria and validation data will be sent to the FDA within 6 months of the action letter date.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

The drug substance Apremilast is a phospodiesterase (PDE4) inhibitor that works intracellularly to modulate a network of pro-inflammatory and anti-inflammatory mediators. Since pro- and anti-inflammatory mediators have been implicated in psoriatic disease, apremilast is proposed in the treatment of active psoriatic arthritis. Apremilast is a white to pale yellow powder with (b) (4). The Biopharmaceutics Classification System places this compound in case which low solubility/low permeability. The (b) (4) the (S)-enantiomer of Apremilast.

(2) Drug Product

The drug substance is formulated with compendia grade excipients to form immediate release 10, 20 and 30 mg tablets. (b) (4). The tablets are prepared (b) (4) The tablets are coated with (b) (4). Apremilast is currently a diamond shaped, film coated tablets in the following dosage strengths: 10 mg pink tablet engraved with "APR" on one side and "10" on the other side; 20 mg brown tablet engraved with "APR" on one side and "20" on the other side; 30 mg beige tablet engraved with "APR" on one side and

"30" on the other side. The proposed expiration date is [redacted] (b) (4) and the storage conditions is 30 °C or below.

B. Description of How the Drug Product is Intended to be Used

Apremilast drug product is intended to be used for the treatment of adult patients with active psoriatic arthritis. The recommended dose is a 30 mg tablet taken twice daily orally. Before the patient starts this regimen, a titration schedule is used. For day 1, a 10 mg tablet is used in the morning. Day 2, 10 mg is used in the morning and evening. Day 3, 10 mg in the morning and 20 mg in the evening. Day 4, 20 mg in the morning and evening. Day 5, 20 mg in the morning and 30 mg in the evening. Day 6 & after, 30 mg in the morning and evening.

C. Basis for Approvability or Not-Approval Recommendation

The application is currently recommended as approvable pending comments from compliance, microbiology, biopharmaceutics and the CMC IR comments that have been sent to the sponsor. The sponsor has provided adequate information in the manufacturing for the drug substance and drug product. Clarifications are need for some of the manufacturing process parameters and analytical methods.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Ciby J. Abraham, Ph.D., CMC Reviewer
Prasad Peri, Ph.D., Branch Chief
Eric Duffy, Ph.D., Division Director

C. CC Block

OB/DBII/RAbugov
ODEII/DPARP/KHull
OCP/DCPII/SAgarwal
OPDP/DPP/PRG3/AAdeleye
OMP/DDMAC/OSalis
ODEII/DPARP/LLeshin
OSEIO/RAS/NRashid
OGD/OGDIO/NSweeney
ONDQA/YLiu
ODEII/DPARP/MGarner
ODEII/DPARP/SSeymour
ONDQA/Biopharm/MHughes
ONDQA/DNDQA3/CBertha

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/s/

CIBY J ABRAHAM
11/20/2013

PRASAD PERI
11/20/2013
I concur

INSPECTIONAL ASSIGNMENT
(EMAIL TRANSMITTAL)

Date:	10/18/13
To:	Investigations Branch Division of Medical Products and Tobacco Inspections Office of Regulatory Affairs
Facility:	CELGENE INTERNATIONAL SARL ROUTE DE PERREUX 1 BOUDRY, CHE FEI No.: 3006323509
Drug Name (dosage form, strength/concentration):	Apremilast Tablets, 10, 20, 30mg
Profile Class:	TCM
A/NDA No.:	NDA 205437/000
Chemistry Reviewer	Ciby Abraham OMPT/CDER/OPS/ONDQA/DNDQAIII/BRVIII 301-796-0612
Microbiology Reviewer (if applicable)	N/A
OC Compliance Officer	Mahesh Ramanadham OMPT/CDER/OC/OMPQ/DGMPA/NDMAB 301-796-3272

CDER has identified specific area(s) for inspectional focus for drug product manufacturing in connection with the NDA 205437/000. In accord with the Drug Process Inspections Compliance Program 7356.002 and the Pre-Approval Inspection Program Compliance Program 7346.832, PAIs provide for continuity in our pre-market review of drug substance by focusing on areas in which data is questionable; drug characteristics or sensitivities[1] indicate special scrutiny, the overall manufacturing and control strategy appears lacking; and potential manufacturing weaknesses may exist.

Summary of Product and Manufacturing Process

[1] Examples include heat, moisture, oxygen, or light sensitivity, as well as hygroscopicity, polymorphs, particle size,

Product:

Apremilast is indicated for the treatment of Active Psoriatic Arthritis and will be used in an immediate release, film coated tablet available in 10, 20, and 30mg. Apremilast tablets will be packaged in (b) (4) blisters with aluminum push through foil and in HDPE bottles. Tablets will be film coated (b) (4) 10mg: pink, 20mg: brown, 30mg; beige.

Apremilast is a Biopharmaceutical Classification System (BCS) Class IV compound and is practically insoluble in water (7 µg/mL at room temperature). The drug substance is manufactured by (b) (4) Celgene Chemicals GmbH, Zofingen Switzerland.

The drug product formulation has changed during development however comparative dissolution studies demonstrated near equivalent dissolution performance between these dosage forms.

Table 1: Summary of Apremilast Formulations Used in Clinical Studies

Formulations	Clinical Studies
Formulated capsules	Phase 1 and 2
White round film-coated tablets	Phase 1 and 2
Modified diamond shape film-coated tablets (pink/brown/beige)	Phase 2 and 3

The sponsor performed an initial risk assessment and conducted numerous DOE studies to determine material attribute impact to product quality attributes. The final result is provided in appendix 1 and demonstrates that material attribute variability is expected to have low impact on product quality, based on the material attribute ranges evaluated. It should be determined if this assessment has been substantiated at commercial scale and if the firm has procedures in place to continually monitor the effect of material attribute variability on product quality. See the included appendices for the following information:

Appendix 1: Drug product DOE and material variability impact assessment
Appendix 2: Drug product critical quality attributes
Appendix 3: Drug product manufacturing control strategy
Appendix 4: NIR method and sample spectrum
Appendix 5: In-process tests
Appendix 6: Finished product specifications
Appendix 7: Batch formula

Manufacturing Process:

(b) (4)

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/s/

MAHESH R RAMANADHAM
10/18/2013

Initial Quality Assessment (IQA) and Filing Review for Pre-Marketing Applications (CMC)

APPLICATION INFORMATION

1. NEW DRUG APPLICATION NUMBER: 205437

2. Drug Name: apremilast tablets (proposed proprietary name: Otezla)
   Drug is an NME
   Applicant: Celgene Corporation (Warren, NJ)

3. RECEIVED DATE: 3/21/2013

4. RELATED REVIEW DOCUMENTS:

   a. Drug Master Files listed on 356h form:

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	III		(b) (4)	10/17/2011	LOA does not provide dates/page numbers of specific submission(s)
	III			6/27/2012	
	III			10/31/2011	LOA does not provide dates/page numbers of specific submission(s)
	III			6/27/2012	
	III			6/27/2012	LOA does not provide dates/page numbers of specific

					submission(s)
(b) (4)	III		(b) (4)	10/28/2011	
	III			6/27/2012	
				6/27/12	
	IV			8/14/2012	Section 1.4.1 of the NDA lists DMF (b) (4) but the LOA provided in the link is for DMF (b) (4) DMF (b) (4) is incorrect and the listing should be corrected in the NDA.
	III			11/04/2011	LOA does not provide date of submission(s).

b. Recommended Consults

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics	☐	X	The applicant claims that no degradation is found on stability
Clin Pharm	☐	X	
EES	X	☐	EES was submitted to compliance on 4/10/2013
Pharm/Tox	X	☐	See 3.2.S.3 for structures of impurities. Many have structure alerts that are related to the drug substance. (b) (4) is the only impurity for which the applicant has performed an in-silico evaluation for genotoxicity (reference is made to section 2.4).
Methods Validation	X	☐	At least one method should be validated (e.g., impurity method) since this is an NME.

EA	☐	X	to be assessed by reviewer.
New Drug Micro	X	☐	re: microbial limits specification, and lack of method in NDA (other than reference to USP).
CDRH	☐	X	
Other	☐	X	

c. Other Applications or Submissions to note (if any):

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
IND		101761	apremilast for treatment of (b) (4).
IND		(b) (4)	(b) (4)

d. Previous Communications with the Applicant to note (if any):
See filing table later in this document.

OVERALL PRODUCT QUALITY CONCLUSIONS AND RECOMMENDATIONS

Is the Product Quality Section of the application fileable from a CMC perspective?		
Yes	No	CMC Filing Issues
X	☐	None.

Are there potential CMC review issues to be forward to the Applicant with the 74 day letter?		
Yes	No	
X	☐	**The following comments pertain to the drug substance.** Add a detailed description of the drug substance manufacturing process in section 3.2.S.2.2. This pertains to section 3.2.S.2.3. Provide more details of methods for starting materials, and summary validation data as a minimum. Specifications for many reagents and solvents only consist of appearance and identity attributes. This is insufficient. If you rely on certificates of analysis (CoAs) in order to assure the quality of these materials, provide them, and provide details of test methods to periodically independently validate the accuracy of the CoAs. Provide more detailed information pertaining to the methods used in section 3.2.S.2.4 and at least summary validation data. You have only provided a short method summary for each analytical procedure in the controls for the drug substance (3.2.S.4.2). Provide detailed analytical methods sufficient to allow their accurate reproduction by FDA laboratories. Develop and implement, at least, a qualitative specification and

method for (b) (4) the drug substance. Alternatively, demonstrate that your FT-IR identification test (b) (4)

Provide the profiles of residual solvents in the drug substance across the different manufacturing processes used in drug substance development.

The following comments pertain to the drug product:

Provide the excipient specifications, even if they are compendial, along with certificates of analysis (CoAs) for the excipients. Your specifications should indicate what specifications are applied on receipt of the excipients, and what specifications are used to periodically validate the data on the certificates of analysis. This latter comment also applies to the (b) (4) materials.

Include a detailed manufacturing description for the proposed commercial process in Section 3.2.P.3.3, including the packaging and labeling processes. Alternatively, Section 3.2.P.3.3. may cross reference detailed information (e.g. specific batch records) provided in Section 3.2.R.

Provide a master batch record (or an executed batch record) for each strength product for each commercial site, or else provide comparably detailed descriptions for each site. Provide a list of any substantive differences between the sites, for manufacturing and control processes for pilot (b) (4)) and commercial batches.

Provide in Section 3.2.P.7 of your NDA, illustrations of each container closure system proposed, and provide dimensional information.

Justify the lack of a drug product specification for (b) (4).

Include an appropriate "related impurities" specification for any unspecified degradation product (NMT 0.1%). Specify individual impurities which may be present at levels greater than 0.10% in the specification (at least by relative retention time, for example).

Provide complete descriptions of all of the analytical procedures for the drug product so that they may be reviewed, and reproduced in an FDA laboratory. Provide the details of the compendial microbial limits

		method as performed for this NDA. Provide updated long term and accelerated stability data for the three proposed commercial drug product manufacturing sites, as soon as it is available. If these data are provided too late in the review cycle, they may or may not be able to be reviewed, depending on our available resources. Provide a methods validation package in accordance with the FDA's "Guideline for Submitting Samples and Analytical Data for Methods Validation." Revise the container label so that it indicates where the lot number and expiry date will be printed.

Is the Product Quality Section of the application fileable from a biopharmaceutics perspective?		
Yes	No	Biopharmaceutics Filing Issues
☐	☐	See separate Biopharmaceutics Review

Are there potential biopharmaceutics review issues to be forward to the Applicant with the 74 day letter?		
Yes	No	
☐	☐	See separate Biopharmaceutics Review

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ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications

NDA #205437: Received Date: 3/21/2013

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
1.	Is the CMC section organized adequately?	X	☐	☐	
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X	☐	☐	
3.	Are all the pages in the CMC section legible?	X	☐	☐	
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included? -See Comment	☐	☐	☐	The information previously requested appears to be mostly review issues rather than filing issues. The CMC reviewer may evaluate the information provided as necessary: see section 1.6.3 (Module 1). Information was provided in response to FDA IR requests (see amendments dated 1/06/09 and 1/08/09 for IND 101761.). Feb. 14, 2011 is the amendment for a stability - special protocol assessment (SPA). FDA agreed with the SPA in a 3/31/11 letter. (b) (4) – CMC meeting minutes with some agreement on drug substance starting materials (see IND (b) (4) for certain information). Agreement on commercial manufacturing sites was supposedly reached per an e-mail dated 7/13/12, however this is not found in DARRTS for IND 101761. See FDA's preliminary comments on QbD proposals (FDA's 12/5/12 letter).

B. FACILITIES*					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
5	Is a single, comprehensive list of all involved facilities available in one location in the application?	x	☐	☐	form FDA 356h
6	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**	☐	☐	X	
7	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X	☐	☐	

8	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X	☐	☐	
9	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X	☐	☐	
1	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X	☐	☐	per individual check boxes for the facilities listed on form 356h.

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	X	☐	☐	A claim of categorical exclusion has been made per 21 CFR 25.31(b), and with the statement that to the best of their knowledge, no extraordinary circumstances exist. See section 1.12.14.

D. MASTER FILES (DMF/MAF)					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
12.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X	☐	☐	*See table on cover page.* There is no drug substance DMF reference, the CMC information is provided in the NDA. Solid oral dosage form container closure components (for bottles and for blisters) have LOAs for their DMFs. The reviewer should verify that the LOAs are present in the respective DMFs.

E. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
13.	Does the section contain a description of the DS manufacturing process?	X	☐	☐	A brief 3 page summary is provided in 3.2.S.2.2. The applicant should place a detailed description of the manufacturing process in this section. Note that section 3.2.S.2.6 indicates that the drug substance process has been improved over the course of development: (b) (4) There is a comparison of impurity profiles of each process: the overall quality of the drug substance (including, e.g., levels of residual solvents) should be shown to be equivalent across these changes (the reviewer should check on this).
14.	Does the section contain identification and controls of critical steps and intermediates of the DS(in process parameters?	X	☐	☐	Note that under 3.2.S.2.3, very little information is provided about the methods used to test starting materials and other raw materials. These methods should be described, along with summary validation data, at least. Specifications for many reagents, and solvents only consist of appearance and identity attributes. Certificates of analysis (CoAs) should be provided for raw materials and solvents, and test methods should be available to periodically independently validate the accuracy of the CoAs. Section 3.2.S.2.4 provides a brief discussion of the control of critical steps and intermediates (3 pages): we should ask for detailed information about the methods used for these controls and their validation data.
15.	Does the section contain information on impurities?	X	☐	☐	Of the impurities discussed, apparently only (b) (4) and impurities (b) (4) have been observed at some level in the drug substance. Note that these impurities (b) (4)
16.	Does the section contain information regarding the characterization of the DS?	X	☐	☐	Yes, and this includes the results of single crystal x-ray analysis, among other techniques.

17.	Does the section contain controls for the DS?	X	☐	☐	Specifications are provided, however, only a short method summary is provided for each analytical procedure. The complete analytical methods should be provided in Section 3.2.S.4.2.
18.	Has stability data and analysis been provided for the drug substance?	X	☐	☐	12 months long term and 6 month accelerated stability data are provided for three primary stability batches (at least 1/5 commercial scale of the proposed commercial process). These batches were produced at Celgene Chemicals GmbH using (b) (4) Also, 6 months long term and accelerated stability data are provided for one production scale batch (b) (4) at the proposed commercial site (b) (4)); this batch was used as a clinical batch. The attributes tested include the following: appearance, (b) (4), assay (HPLC), related impurities (HPLC), (b) (4) and chiral purity by HPLC. Also, stability data are reported (one month timepoint) for the validation batches manufactured at (b) (4). Appearance, assay and related impurities are the attributes that are being tested for the post approval stability protocol studies that are underway. *The reviewer should determine whether the reduced attributes studied under the stability commitment are sufficient.*
19.	Does the application contain Quality by Design (QbD) information regarding the DS?	X	☐	☐	See 3.2.S.2.6, manufacturing process development.
20.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?	☐	X	☐	
21.	Does the section contain container and closure information?	X	☐	☐	Minimal information is provided. Drug substance is stored in (b) (4) The container closure components are said to comply with the applicable FDA indirect food additive regulations (21 CFR Parts 172-178).

F. DRUG PRODUCT (DP)					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
22	Does the section contain quality controls of excipients?	X	☐	☐	All excipients are indicated to be compendial (USP/NF) except for the (b) (4). No additional specifications are listed for the compendial excipients. The applicant should provide the excipient specifications, even if they are compendial, along with certificates of analysis for the excipients. They should indicate what specifications are applied on receipt of the excipients, and what specifications are used to periodically validate the data on the certificates of analysis. This latter comment also applies to the (b) (4) materials.
23	Does the section contain information on composition?	X	☐	☐	Batch formulae are also provided for product from the Celgene International site (10 mg, 20 mg, 30 mg tablets, with batch sizes from (b) (4) tablets, depending on strength) and for product from the (b) (4) (10 mg, 20 mg, 30 mg tablets, batch sizes from (b) (4) tablets, depending on strength). Therefore, there are three manufacturing sites for d.p. being proposed.
24	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X in part	☐	☐	The information provided is inadequate for section 3.2.P.3.3: there is a flow diagram of the process and a very brief description of the process, which doesn't include filling, labeling and packaging. A detailed manufacturing description for the proposed commercial process should be included in Section 3.2.P.3.3, including packaging and labeling. Alternatively, reference may be made to site specific batch records in 3.2.R., which also should be provided.

25	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X	☐	☐	Only one critical process parameter (CPP) is listed as a manufacturing in process control (IPC): namely, [redacted] (b) (4) This CPP was said to have been identified through QbD studies. Tablet hardness is another IPC, but it is not indicated to be a CPP. No drug product intermediates are identified.
26	Is there a batch production record and a proposed master batch record?	X	☐	☐	In section 3.2.R, there is a single batch record, marked for clinical phase III studies, manufactured at a scale of [redacted] (b) (4) tablets by [redacted] (b) (4). It is for 30 mg tablets. There are no batch records for other strengths or for commercial sites. Master batch records should be provided for each strength product for each commercial site, or else comparably detailed descriptions. The applicant should provide a list of any substantive differences in the manufacturing and control processes between the sites, for pilot [redacted] (b) (4) and commercial batches.

27	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X	☐	☐	Phase 1 began with capsules, then [redacted] (b) (4) tablets were developed, and both of these dosage forms were used in both Phase 1 and Phase 2 studies. A comparative bioavailability study was conducted to compare the relative bioavailability of the tablets versus capsules. During phase 2, the tablets were modified to a "Phase 3 image": the [redacted] (b) (4) tablets and phase 3 tablets. The modifications appear to involve [redacted] (b) (4) The color varies with the strength of the tablets (10 mg tablets are pink, 20 mg tablets are brown, 30 mg tablets are beige) [redacted] (b) (4) and the differences between the [redacted] (b) (4) tablets and the phase 3 tablets "do not affect the release profile of the immediate release dosage form and therefore an in vivo bioequivalence study is not deemed necessary." Finally, a change is proposed to the commercial product formulation relative to the phase 3 formulation. [redacted] (b) (4) the applicant claims that the phase 3 tablets maintained their purity, potency and dissolution characteristics. The commercial product will have different [redacted] (b) (4) and are made by "essentially the same manufacturing process and have the same [redacted] (b) (4) as the Phase 3 tablets." Comparability between the Phase III and commercial tablets is supported by a bracketed study: 10 mg and 30 mg tablets were subject to an *in vitro* comparative dissolution study in three different pH media. It is noted that the capsule formulation originally [redacted] (b) (4); the applicant states that the [redacted] (b) (4) See comments for applicant in item 26, above.
28	Have any biowaivers been requested?		☐	☐	[See separate Biopharmaceutics review]

29	Does the section contain description of to-be-marketed container/closure system and presentations?	X	☐	☐	These are incomplete. There are two different packaging formats for the drug product: blister packages and bottles. Some bottles (b) (4) Section 3.2.P.7 does not show any illustrations of the bottles or the blister packaging, although it lists the component materials and provides DMF references for each material. Comment for applicant: Provide in Section 3.2.P.7 of your NDA, illustrations of each container closure system proposed, and provide dimensional information.
30	Does the section contain controls of the final drug product?	X	☐	☐	It is noted that there is no specification for (b) (4) the applicant should justify this. Impurities at levels greater than 0.10% should be specified in the specification (at least by relative retention time, for example). The applicant should include a "related impurities" specification for any unspecified degradation product (NMT 0.1%). It may be noted that "to date, no degradation products [are] observed in apremilast tablets." Comments on analytical procedures: the full analytical procedure is not provided, but instead, brief summaries of the methods are provided. The method for microbial limits is not provided, it is just referenced to USP <61> and <62>, or to Ph. Eur. Note that there is a NIR procedure (as an alternate content uniformity method) which is also inadequately described in 3.2.P.5.2 (although more information is provided in the validation report) and which needs specialized assessment within ONDQA. Provide complete descriptions of all of the analytical procedures for the drug product so that they may be reviewed, and reproduced in an FDA laboratory. Provide the details of the compendial microbial limits method as performed for this NDA. Method validation reports do not provide all of the data generated during validation, some data summaries are given in lieu of the full data (e.g., methods for dissolution, assay, related impurities & content uniformity). *It isn't clear whether additional information and data are needed for the alternate NIR method for content uniformity: this should be evaluated by a reviewer with NIR expertise.* The batch data provided are somewhat summarized: e.g., dissolution is given at 4 time points, but only the mean, min and max data are given at each time point. Individual data are not provided at all for content uniformity, only the mean and the acceptance value. This is a review issue as there is a possibility that these data could be sufficient.

31	Has stability data and analysis been provided to support the requested expiration date?	X	☐	☐	Three primary stability batches of each strength (10 mg, 20 mg, 30 mg) were manufactured at (b) (4) (manufacturer of clinical supplies). The applicant claims that they used the proposed commercial process at greater than one tenth the commercial scale. Stability data is up to 12 months long term (30°C/65%RH) and 6 months accelerated (40°C/75% RH) for these primary batches. Product presentations included in the primary stability data include (b) (4) blisters, and HDPE bottles (60, (b) (4) tablets per bottle). A (b) (4) design was used for the stability studies of the bottles, said to be based on an Agency approved (3/31/11) Special Protocol Assessment. [See item #4, above] For these primary stability batches, both for blisters and bottles, the commercial image is said to have been used. Proposed drug product commercial manufacturing sites include the following: Celgene International Sarl (Boudry, Switzerland), (b) (4) These data were also collected using a (b) (4) design. No stability data is provided for the (b) (4), other than release data. For Celgene International, there is very limited stability data (3 months), one batch per strength, plus release data only from another batch per strength. Not all presentations are studied for each batch of bottled product: drug product presentations are (b) (4) these data. Two batches of product per strength were studied in (b) (4) blisters, for a maximum of 3 months so far. No stability data are provided for the (b) (4) site, only release data for one batch per strength, two product presentations (bottles) per strength, also two batches per strength for (b) (4) blisters. This appears to be acceptable, as release data has been provided for these commercial drug product sites. In addition, it is not a current ONDQA policy in general to require site specific stability data (unless there is some justification). Photostability data are available. The proposed shelf life (expiry) for the drug product is (b) (4) (with storage below 30°C). A statistical stability analysis has not been found in this NDA, however it may not be necessary: the applicant states that (based on data provided so far) "There is no evidence of any trends in degradation in samples stored under long term or accelerated conditions." *The reviewer should verify this statement in the data provided.*

32	Does the application contain Quality by Design (QbD) information regarding the DP?	X See Comment	☐	☐	Minimal – per input from Sharmista Chatterjee. The following elements are provided: design space for drug substance, wide ranges for [redacted] (b) (4) (drug product), and an alternative drug product method for content uniformity which utilizes Near IR.
33	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	☐	X	☐	Not observed.

G. METHODS VALIDATION (MV)					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
34.	Is there a methods validation package?	☐	x	☐	We should request a methods validation package in accordance with the FDA's "Guideline for Submitting Samples and Analytical Data for Methods Validation." Because this is an NME, there should be at least one method validated (e.g., an impurities method) by FDA laboratories.

H. MICROBIOLOGY					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
35.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?	☐	☐	X	

I. LABELING					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
36.	Has the draft package insert been provided?	X	☐	☐	
37.	Have the immediate container and carton labels been provided?	X	☐	☐	Carton and container label says to take by mouth; this would seem to cover the need to specify oral administration. Container label does not have a designated space for lot number and expiry date.
38.	Does section contain tradename and established name?	☐	X	☐	Established name is provided, tradename is not yet agreed upon.

J. FILING CONCLUSION					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
39.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	X	☐	☐	
40.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.	☐	☐	☐	Describe filing issues here or on additional sheets
41.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	X	☐	☐	See near front of the IQA review document.

REVIEW AND APPROVAL

This document will be signed in DARRTS by the following:

CMC Lead
Branch Chief

{See appended electronic signature pag

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

/s/

ALAN C SCHROEDER
04/30/2013

PRASAD PERI
04/30/2013
I concur