CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205382Orig1s000

CHEMISTRY REVIEW(S)

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

F hment:	**CFN:** (b) (4) **FEI:** (b) (4)		
	(b) (4)		
	(b) (4)		
DMF No:	26339	**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
	DRUG SUBSTANCE RELEASE TESTER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	25-MAR-2014		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:** (b) (4) **FEI:** (b) (4)		
	GLAXOSMITHKLINE (b) (4)		
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE STABILITY TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
I estone:	OC RECOMMENDATION		
M. .one Date:	11-OCT-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:** (b) (4) **FEI:** (b) (4)		
	GLAXOSMITHKLINE INC		
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE STABILITY TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	06-NOV-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Reference ID: 3503301

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 205382/000	**Sponsor:**	GLAXO GRP ENGLAND
Org. Code:	570		
Priority:	5		**BRENTFORD, MIDDLESEX UB6 0NN, UNITED I**
Stamp Date:	30-APR-2013	**Brand Name:**	(b) (4) (TM) ELLIPTA (TM)
PDUFA Date:	30-APR-2014	**Estab. Name:**	UMECLIDINIUM BROMIDE
Action Goal:		**Generic Name:**	
District Goal:	30-NOV-2013	**Product Number; Dosage Form; Ingredient; Strengths**	001; POWDER, FOR INHALATION; UMECLIDINIUM; 62.5MCG

FDA Contacts:	A. SHAW	Prod Qual Reviewer		3017961460
	Y. LIU	Product Quality PM		3017961926
	A. RAMSEY	Regulatory Project Mgr	(HFD-570)	3017962284
	ID = 105168	Team Leader		

Overall Recommendation:	ACCEPTABLE	on 25-MAR-2014	by R. SAFAAI-JAZI	()	3017964463
	PENDING	on 15-MAY-2013	by EES_PROD		
	PENDING	on 15-MAY-2013	by EES_PROD		

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

GLAXO OPERATIONS (b) (4)
(b) (4)

(b) (4)

DMF No: **AADA:**

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

Profile:	AEROSOL DISPERSED MEDICATION	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	20-AUG-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	20-AUG-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Reference ID: 3503301

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/s/

SHANNON J CREWS
05/08/2014

Chemistry Review Cover Sheet

INCRUSE ELLIPTA
(Umeclidinium bromide)
Craig Bertha, Ph.D. Drug Substance Review
Arthur B. Shaw, Ph.D. Drug Product Review
DNDQA III/Branch VIII/DPARP

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Reference ID: 3477186

Chemistry Review Data Sheet

1. NDA 205382

2. REVIEW #:2

3. REVIEW DATE: March 25, 2014

4. REVIEWER: Arthur B. Shaw, Ph.D.

5. PREVIOUS DOCUMENTS:

Document	Document Date	Comment
Original	2013-04-29	
Filing review	2013-05-31	Acceptable
IR Letter	2013-09-26	Request for information about APSD stat and DCU
Quality Amendment	2013-10-17	Response to IR letter
Stat Consult Request	2013-10-17	Stat evaluation of amendment
Stat Consult Request	2013-10-23	Additional stat evaluation of amendment
Stat review	2013-11-14	Review of APSD stats
IR Letter	2013-11-21	A number of issues
Stat review	2013-12-02	Review of Emitted Dose starts
Stat review	2013-12-02	review of Emitted Dose plan
Quality Amendment	2013-12-04	Response to IR 2013-11-21
Chem review #1	2013-03-20	Approvable pending satisfactory inspection

6. SUBMISSION(S) BEING REVIEWED:

Document	Document Date	Comment
Establishment evaluation Report	2014-03-24	All sites satisfactory. Report attached

7. NAME & ADDRESS OF APPLICANT:
Glaxo Group Limited, England d/b/a GlaxoSmithKline
980 Great West Road
Brentford
Middlesex TW89GS
United Kingdom

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Incruse Ellipta
   b) Non-Proprietary Name (USAN): umeclidinium bromide
   c) Code Name/# GSK573719
   d) Chem. Type/Submission Priority
      - Chem. Type: 2
      - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)
10. PHARMACOL. CATEGORY: Anticholinergic

11. DOSAGE FORM: Powder

12. STRENGTH/POTENCY: 62.5 µg

13. ROUTE OF ADMINISTRATION: Inhalation

14. Rx/OTC DISPENSED: _X__Rx ___OTC

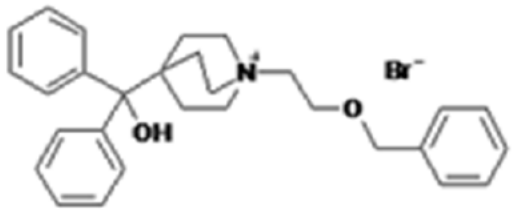
Reference ID: 3477186

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): No

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

Umeclidinium bromide

1-[2-(benzyloxy)ethyl]-4-(hydroxydiphenylmethyl)-1-azoniabicyclo[2.2.2]octane bromide



$C_{29}H_{34}NO_2 \bullet Br$

MW = 508.5

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF	Type	Holder	Subject	Review Status
26339	II	GSK	Umeclidinium Bromide	Acceptable 03/29/2013
(b) (4)	III	(b) (4)	(b) (4)	Acceptable 12/21/2012

The following DMFs do not need review because there is sufficient information in the NDA. These are:

DMF #	Type	Holder	Item
(b) (4) (b) (4)	IV	(b) (4)	(b) (4)
	III		
	III		
	III		
	III		
(b) (4)	III	(b) (4)	

B. Related Documents

IND-104479 GSK573719 inhalation powder

IND- (b) (4) GSK573719 /GW642444 Inhalation Powder

In addition, GSK has an NDA 203975 (approved 12/17/2013) for umeclidinium bromide/vilanterol trifenatate, using the (b) (4) blister packaging, inhaler, and secondary packaging.

Reference ID: 3477186

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	03/24/2014	
EA	Categorical Exclusion granted		
Microbiology	Approval	04/03/2013	E. Pfeiler
Statistics	Recommend tighten APSD See discussion below Emitted Dose content Uniformity Acceptable	11/14/2013 12/04/2013	X. Dong
Methods Validation	Not necessary		
Biopharmaceutics review	Acceptable	06/14/2013	O.Eradiri

Reference ID: 3477186

The Chemistry Review for NDA 205382

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application may be approved from a CMC point of view.

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

None

II. Summary of Chemistry Assessments

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

1. Drug Substance

Umeclidinium bromide was recently approved in NDA 203975 (12/17/2013) and is designed to be an anticholinergic. It is a white solid that is slightly soluble in water and in simulated gastric and intestinal fluids. It is present in a [redacted] (b) (4) with no polymorphs. Although the most distinct absorbance maximum is at [redacted] (b) (4), there is a [redacted] (b) (4) with a higher molar absorptivity. Detection in HPLC systems is done near this wavelength. It is slightly hygroscopic. It is provided in a micronized form. The complete CMC information is provided in DMF 26339, which is held by the applicant, GlaxoSmithKline. The DMF was reviewed by Craig Bertha and found adequate on March 29, 2013. It is very stable, although forced degradation studies have identified potential degradants. The impurities in the drug substance are due to the synthesis. The applicant has identified a number of CQAs that are well-controlled. All sites have a satisfactory cGMP status.

2. Drug Product

The drug product is intended to be delivered to the lungs of patients with Chronic Obstructive Pulmonary Disease (COPD). These patients have compromised respiratory systems so the drug must be able to be delivered to the lung with minimum effort by the patient. The inhaler was shown to perform correctly independent of the severity of the patient's disease. Building on experience with previously approved dry powder inhalers, the applicant has developed a formulation and delivery system that delivers the drug as a dry powder, to be inhaled through a specially designed inhaler, equipped with a dose counter. [redacted] (b) (4). Magnesium stearate is added to the blend to [redacted] (b) (4). The powder is filled into blister strips (30 count and 7 count) which are assembled into inhalers. The drug product of this application includes a single blister strip containing the drug product formulation. Each inhaler is provided in a foil-covered tray to maintain a constant environment for the inhalers during storage. Once the inhaler is removed by the patient it is exposed to the

Reference ID: 3477186

environment. The entire system is designed to deliver a therapeutic dose of drug in the aerodynamic size range of (b) (4). Control of the Aerodynamic Particle Size Distribution (APSD) ensures a consistent delivery of a therapeutic dose of the drug substance. The labeled strength of the drug substance is in terms of the (b) (4) and the total amount filled in each blister.

The developmental studies identified the Critical Quality Attributes (CQAs) and experiments were designed to assess the effects of the formulation, the manufacturing process and the container closure system on these CQAs. The CQAs include Identity, Blister content, Degradants, Emitted Dose Content Uniformity, APSD, Foreign particulate Matter, and Microbiological Quality. (b) (4) (b) (4)

Magnesium stearate was (b) (4) (b) (4) (b) (4) (b) (4) The strip is then assembled into the inhaler, which is then placed in a foil tray with a desiccant at (b) (4) and the tray is sealed.

The drug product is very stable, staying within specifications throughout the long-term and accelerated stability studies. The applicant has provided 15 months of long-term stability data to support an expiration date of 24 months. There were no trends in the data so a statistical analysis was not necessary. The applicant proposed that the drug product not be tested for umeclidinium degradants at release, since the drug substance is very stable and there are no steps in the manufacturing that could cause degradation. This is acceptable. Another feature of the release testing is that some tests are performed on the blister strips, other are performed on the inhalers, and others are performed on the finished product. These are justified by the development data. In addition, the applicant has a two-tier test for microbiological quality. The first tier is a test for water activity. Since water is needed for the growth of most microorganisms a low water activity can be used as a surrogate for actually measuring microbiological contamination. If the sample fails the water activity test, then the standard microbial limits test will be used. This was found acceptable by the Microbiologist. In-use studies, in which the inhaler was removed from its secondary packaging, after storage at 25C/60%RH, showed that the drug product was stable out of its secondary packaging for up to three months. This supports the label instructions to discard the inhaler after six weeks out of the secondary packaging.

All sites have a satisfactory cGMP status.

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

The drug product is intended for daily use by patients with Chronic Obstructive Pulmonary Disease (COPD. The drug is designed to be inhaled using a custom inhaler and with minimal patient effort. The basic operation steps involve opening the mouthpiece cover, inhaling the drug through the mouthpiece and closing the device mouth cover.

Reference ID: 3477186

C. **Basis for Approvability or Not-Approval Recommendation**
The NDA may be approved based on adequate CMC data to ensure that the drug product delivers the correct therapeutic doses of the drug substance consistently throughout the proposed shelf life and during use by the patient outside of the secondary packaging.

III. Administrative

A. Reviewer's Signature See DARRTS

B. Endorsement Block: See DARRTS

Reference ID: 3477186

Review of Common Technical Document-Quality (CTD-Q) Module 3.2: Body of Data

S DRUG SUBSTANCE: ACCEPTABLE See Chem Review #1

P DRUG PRODUCT ACCEPTABLE See Chem Review #1

A APPENDICES N/A

R REGIONAL INFORMATION ACCEPTABLE See Chem Review #1

A. Review of Common Technical Document-Quality (CTD-Q) Module 1 ACCEPTABLE See Chem Review #1

B. Environmental Assessment or Claim of Categorical Exclusion Requested and granted.

C. List of Deficiencies and Comments to Be Communicated to Applicant: None

Reference ID: 3477186

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/s/

ARTHUR B SHAW
03/25/2014
Added satisfactory EER

PRASAD PERI
03/26/2014
I concur

Chemistry Review Cover Sheet

INCRUSE ELLIPTA
(Umeclidinium bromide)
Craig Bertha, Ph.D. Drug Substance Review
Arthur B. Shaw, Ph.D. Drug Product Review
DNDQA III/Branch VIII/DPARP

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1. Drug Substance 6

2. Drug Product 6

B. Description of How the Drug Product is Intended to be Used 7

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A. Labeling & Package Insert: 137

B. Environmental Assessment or Claim of Categorical Exclusion Requested and granted. 138

C. List of Deficiencies and Comments to Be Communicated to Applicant: None 138

Reference ID: 3448038

Chemistry Review Data Sheet

1. NDA 205382
2. REVIEW #:1
3. REVIEW DATE: March 14, 2014
4. REVIEWER: Arthur B. Shaw, Ph.D.
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

Document	Document Date	Comment
Original	2013-04-29	
Filing review	2013-05-31	Acceptable
IR Letter	2013-09-26	Request for information about APSD stat and DCU
Quality Amendment	2013-10-17	Response to IR letter
Stat Consult Request	2013-10-17	Stat evaluation of amendment
Stat Consult Request	2013-10-23	Additional stat evaluation of amendment
Stat review	2013-11-14	Review of APSD stats
IR Letter	2013-11-21	A number of issues
Stat review	2013-12-02	Review of Emitted Dose starts
Stat review	2013-12-02	review of Emitted Dose plan
Quality Amendment	2013-12-04	Response to IR 2013-11-21

7. NAME & ADDRESS OF APPLICANT:
Glaxo Group Limited, England d/b/a GlaxoSmithKline
980 Great West Road
Brentford
Middlesex TW89GS
United Kingdom

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Proposed: Incruse Ellipta
   b) Non-Proprietary Name (USAN): umeclidinium bromide
   c) Code Name/# GSK573719
   d) Chem. Type/Submission Priority
      - Chem. Type: 2
      - Submission Priority: S

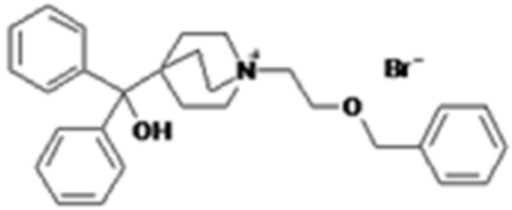
9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)
10. PHARMACOL. CATEGORY: Anticholinergic
11. DOSAGE FORM: Powder
12. STRENGTH/POTENCY: 62.5 µg
13. ROUTE OF ADMINISTRATION: Inhalation
14. Rx/OTC DISPENSED: _X__Rx ___OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): No

Reference ID: 3448038

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

Umeclidinium bromide

1-[2-(benzyloxy)ethyl]-4-(hydroxydiphenylmethyl)-1-azoniabicyclo[2.2.2]octane bromide



$C_{29}H_{34}NO_2 \bullet Br$

MW = 508.5

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF	Type	Holder	Subject	Review Status
26339	II	GSK	Umeclidinium Bromide	Acceptable 03/29/2013
(b) (4)	III	(b) (4)	(b) (4)	Acceptable 12/21/2012

The following DMFs do not need review because there is sufficient information in the NDA. These are:

DMF #	Type	Holder	Item
(b) (4)	IV	(b) (4)	
	III		
	III		
	III		
	III		
(b) (4)	III		

Reference ID: 3448038

B. Related Documents

IND-104479 GSK573719 inhalation powder

IND-106616 GSK573719 /GW642444 Inhalation Powder

In addition, GSK has an NDA 203975 (approved 12/17/2013) for umeclidinium bromide/vilanterol trifenatate, using the [redacted] (b) (4) blister packaging, inhaler, and secondary packaging.

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
EA	Categorical Exclusion granted		
Microbiology	Approval	04/03/2013	E. Pfeiler
Statistics	Recommend tighten APSD See discussion below Emitted Dose content Uniformity Acceptable	11/14/2013 12/04/2013	X. Dong
Methods Validation	Not necessary		
Biopharmaceutics review	Acceptable	06/14/2013	O.Eradiri

Reference ID: 3448038

The Chemistry Review for NDA 205382

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application may be approved from a CMC point of view pending a satisfactory CGMP inspection of one site.

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

None

II. Summary of Chemistry Assessments

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

1. Drug Substance

Umeclidinium bromide was recently approved in NDA 203975 (12/17/2013) and is designed to be an anticholinergic. It is a white [redacted] (b) (4) that is slightly soluble in water and in simulated gastric and intestinal fluids. It is present in a [redacted] (b) (4) form with no polymorphs. Although the most distinct absorbance maximum is at [redacted] (b) (4) there is a [redacted] (b) (4) with a higher molar absorptivity. Detection in HPLC systems is done near this wavelength. It is slightly hygroscopic. It is provided in a micronized form. The complete CMC information is provided in DMF 26339, which is held by the applicant, GlaxoSmithKline. The DMF was reviewed by Craig Bertha and found adequate on March 29, 2013. It is very stable, although forced degradation studies have identified potential degradants. The impurities in the drug substance are due to the synthesis. The applicant has identified a number of CQAs that are well-controlled

2. Drug Product

The drug product is intended to be delivered to the lungs of patients with Chronic Obstructive Pulmonary Disease (COPD). These patients have compromised respiratory systems so the drug must be able to be delivered to the lung with minimum effort by the patient. The inhaler was shown to perform correctly independent of the severity of the patient's disease. Building on experience with previously approved dry powder inhalers, the applicant has developed a formulation and delivery system that delivers the drug as a dry powder, to be inhaled through a specially designed inhaler, equipped with a dose counter. [redacted] (b) (4). Magnesium stearate is added to [redacted] (b) (4). The powder is filled into blister strips (30 count and 7 count) which are assembled into inhalers. The drug product of this application includes a single blister strip containing the drug product formulation. Each inhaler is provided in a foil-covered tray to maintain a constant environment for the inhalers during storage. Once the inhaler is removed by the patient it is exposed to the environment. The entire system is designed to deliver a therapeutic dose of drug in the

Reference ID: 3448038

aerodynamic size range of (b) (4). Control of the Aerodynamic Particle Size Distribution (APSD) ensures a consistent delivery of a therapeutic dose of the drug substance. The labeled strength of the drug substance is in terms of the (b) (4) and the total amount filled in each blister.

The developmental studies identified the Critical Quality Attributes (CQAs) and experiments were designed to assess the effects of the formulation, the manufacturing process and the container closure system on these CQAs. The CQAs include Identity, Blister content, Degradants, Emitted Dose Content Uniformity, APSD, Foreign particulate Matter, and Microbiological Quality. (b) (4) (b) (4)

Magnesium stearate was (b) (4) (b) (4) (b) (4) (b) (4) The strip is then assembled into the inhaler, which is then placed in a foil tray with a desiccant at (b) (4) and the tray is sealed.

The drug product is very stable, staying within specifications throughout the long-term and accelerated stability studies. The applicant has provided 15 months of long-term stability data to support an expiration date of 24 months. There were no trends in the data so a statistical analysis was not necessary. The applicant proposed that the drug product not be tested for umeclidinium degradants at release, since the drug substance is very stable and there are no steps in the manufacturing that could cause degradation. This is acceptable. Another feature of the release testing is that some tests are performed on the blister strips, other are performed on the inhalers, and others are performed on the finished product. These are justified by the development data. In addition, the applicant has a two-tier test for microbiological quality. The first tier is a test for water activity. Since water is needed for the growth of most microorganisms a low water activity can be used as a surrogate for actually measuring microbiological contamination. If the sample fails the water activity test, then the standard microbial limits test will be used. This was found acceptable by the Microbiologist. In-use studies, in which the inhaler was removed from its secondary packaging, after storage at 25C/60%RH, showed that the drug product was stable out of its secondary packaging for up to three months. This supports the label instructions to discard the inhaler after six weeks out of the secondary packaging.

All sites have a satisfactory cGMP status except one site that is scheduled for inspection.

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

The drug product is intended for daily use by patients with Chronic Obstructive Pulmonary Disease (COPD. The drug is designed to be inhaled using a custom inhaler and with minimal patient effort. The basic operation steps involve opening the mouthpiece cover, inhaling the drug through the mouthpiece and closing the device mouth cover.

Reference ID: 3448038

C. **Basis for Approvability or Not-Approval Recommendation**
The NDA may be approved, pending satisfactory inspection results, based on adequate CMC data to ensure that the drug product delivers the correct therapeutic doses of the drug substance consistently throughout the proposed shelf life and during use by the patient outside of the secondary packaging.

III. Administrative

A. Reviewer's Signature See DARRTS

B. Endorsement Block: See DARRTS

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Reference ID: 3448038

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/s/

ARTHUR B SHAW
03/14/2014

CRAIG M BERTHA
03/18/2014

PRASAD PERI
03/20/2014

ONDQA - BIOPHARMACEUTICS
INITIAL PRODUCT QUALITY ASSESSMENT AND FILING REVIEW

NDA Number	205-382
Submission Date	April 30, 2013.
Product name, generic of active(s)	Umeclidinium Bromide
Dosage form and strengths	Powder for Inhalation, 62.5 µg; 30 and 7 blister dose packs
Indication	Maintenance treatment of airflow obstruction in patients with Chronic Obstructive Pulmonary Disease (COPD), including chronic bronchitis and emphysema
Applicant	GSK
Clinical Division	DPP
Type of Submission	505(b)(1) New Drug Application
Biopharmaceutics Reviewer	Okpo Eradiri, Ph.D.
Acting Biopharmaceutics Team Leader	Sandra Suarez, Ph.D.
Acting Biopharmaceutics Supervisor	Richard Lostritto, Ph.D.

SUBMISSION

Umeclidinium, a long-acting muscarinic antagonist and the subject of this NDA, is being proposed by the Applicant for once-daily oral inhalation via a dry powder inhaler in the treatment of patients with COPD. The drug is also the subject of another pending NDA (# 203,975) in which it is combined with a long-acting beta$_2$-agonist, Vilanterol.

PROPOSED DISSOLUTION METHOD

Dissolution testing is not being implemented currently as part of the quality control tests of orally inhaled products (OIPs). Nevertheless, the Applicant used a developmental method to test the dissolution of some batches representative of clinical trial batches, but was not implemented for all the clinical or registration/stability batches. The proposed *in-vitro* dissolution method is presented in Module 3, section 3.2.P.2.2, subsection 3.2 (page 16 – 19 of 26), titled "In Vitro dissolution characteristics of Umeclidinium Inhalation Powder". (b) (4)

PROPOSED DISSOLUTION ACCEPTANCE CRITERION

Dissolution testing is not being implemented for this product and therefore, there is no proposed dissolution acceptance criterion.

Reference ID: 3324844

ONDQA - BIOPHARMACEUTICS
INITIAL PRODUCT QUALITY ASSESSMENT AND FILING REVIEW

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS A. INITIAL OVERVIEW OF THE APPLICATION FOR FILING				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the dissolution test part of the DP specifications?		X	
2.	Does the application contain the dissolution method development report?		X	
3.	Is there a validation package for the analytical method and dissolution methodology?		X	
4.	Does the application include a biowaiver request?		X	
5.	Is there information provided to support the biowaiver request?			N/A
6.	Is there information provided to assess dose dumping in the presence of alcohol?			N/A
7.	Is discriminating power of the dissolution test demonstrated?		X	
8.	Does the application include an IVIVC model?		X	N/A
9.	Is information such as BCS classification mentioned, and supportive data provided?		X	
10.	Is information on mixing the product with foods or liquids included?			N/A
11.	Is there any in *vivo* BA or BE information in the submission?	X		BA studies will be reviewed by OCP.
B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
12.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	X		
13.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.	-	-	The NDA is fileable from a Biopharmaceutics perspective.
14.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	X		None.

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ONDQA - BIOPHARMACEUTICS
INITIAL PRODUCT QUALITY ASSESSMENT AND FILING REVIEW

RECOMMENDATION:

The ONDQA Biopharmaceutics team has reviewed NDA 205382 for filing purposes. We found this NDA **fileable** from a Biopharmaceutics perspective.

Comment to the Review Team

No further Biopharmaceutics review is needed for this NDA because currently *in-vitro* release is not a quality control test for orally inhaled drug products. The *in-vivo* bioavailability and pharmacokinetic studies will be reviewed by OCP. In addition, there are no design space issues to be evaluated.

{See appended electronic signature page}

Okpo Eradiri, Ph.D. Date
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

{See appended electronic signature page}

Sandra Suarez, Ph.D. Date
Acting Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

Reference ID: 3324844

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

/s/

OKPONANABOFA ERADIRI
06/14/2013

SANDRA SUAREZ
06/14/2013

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

APPLICATION INFORMATION

1. NEW DRUG APPLICATION NUMBER: N205382

Umeclidinium bromide is currently an NME, however, a combination product containing this drug substance has already been filed from GSK under NDA 203975. The drug is proposed for maintenance treatment of Chronic Obstructive Pulmonary Disease (COPD).

2. Drug Name: [redacted] (b) (4)™ Ellipta™ (umeclidinium inhalation powder)

There is a single strength of the drug product, with 62.5 mcg of umeclidinium (as the [redacted] (b) (4) per actuation (equivalent to 74.2 mcg of umeclidinium bromide). The blister strip and formulation contained therein, is [redacted] (b) (4) combination drug product of N203975, according to the applicant. [redacted] (b) (4) [redacted] (b) (4) the device is the same as that used for GSK's N203975 and N204275, the latter of which was recently approved.

3. RECEIVED DATE: 30-APR-2013 (Applicant: GlaxoSmithKline or GSK)

4. RELATED REVIEW DOCUMENTS:

a. Drug Master Files listed on 356h form:

DMF #	TYPE	HOLDER	ITEM	LOA DATE	COMMENTS
[redacted] (b) (4)	4	[redacted] (b) (4)	[redacted] (b) (4)	13-FEB-2013	Verify LOA in file; Last reviewed 25-SEP-2012
[redacted] (b) (4)	3	[redacted] (b) (4)		12-APR-2012	Claimed to be the same as those in approved [redacted] (b) (4) products
[redacted] (b) (4)	3	[redacted] (b) (4)		17-DEC-2012	Verify LOA in file; Last reviewed

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					21*DEC-2012
(b) (4)	3	(b) (4)	(b) (4)	24-SEP-2012	Verify LOA in file; Last reviewed 14-DEC-2012
(b) (4)	3	(b) (4)		18-MAR-2013	Verify LOA in file; Last reviewed 25-SEP-2012
26339	2	GSK	bromide	29-NOV-2012	Last reviewed 27-MAR-2013

b. Recommended Consults

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics	X	☐	Request (if necessary) to confirm acceptance of the Parametric Tolerance Interval Test (PTIT) for delivered dose uniformity (DDU) testing (if different from that approved with N204275); Request evaluation of stability data if trends in parameters will limit expiry.
Clin Pharm	☐	X	
EES	X	☐	Submitted to OC by ONDQA
Pharm/Tox	☐	X	(b) (4)
Methods Validation	☐	X	iewer discretion if any drug product methods are questionable, but umeclidinium may not be an NME if N203975 is approved prior to N205382
EA	☐	X	Applicant claims environmental introduction concentration allows exclusion as per 21 CFR 25.31(b); reviewer can evaluate if any data are needed to support claim
New Drug Micro	X	☐	Two tier microbial quality specification proposed with water activity testing (tier 1) and a microbial limit testing (tier 2) (appears similar to what was approved in N204275).
CDRH	☐	X	Device is the same as approved for N204275
Other	X	☐	Reviewer may need consult for Near IR method for determination of water activity if it differs from that for approved N204275

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

DOCUMENT NAME	DATE	APPLICATION	DESCRIPTION

Reference ID: 3316193

		NUMBER	
IND	14-JUL-2009	104479	For COPD indication
IND	13-NOV-2009	106616	For COPD indication
NDA	18-DEC-2012	203975	For COPD indication

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d. Previous Communications with the Applicant to note (see module 1.6.3 for complete detail):

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
Meeting minutes	05 & 07-JUN-2012	IND 106616	CMC aspects of umeclidinium/vilanterol product
Meeting minutes	24-OCT-2010	IND 106616	CMC EOP2 meeting for umeclidinium/vilanterol product

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	☐	1.

Are there potential CMC review issues to be forward to the Applicant with the 74 day letter?		
Yes	No	
☐	X	

Is the Product Quality Section of the application fileable from a biopharmaceutics perspective?		
Yes	No	Biopharmaceutics Filing Issues
☐	☐	To be separately assessed by the biopharmaceutics team

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

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Does the submission contain any of the following elements?

	Yes	No	Comments
Botanical Products	☐	X	
Combination Products	X	☐	
Nanotechnology	☐	X	
PET	☐	X	
QbD Elements	X	☐	
SPOTS	☐	X	

Is a team review recommended?

Yes	No	Suggested expertise for team
☐	X	

CMC Summary:
Critical Issues and Complexities

(This section is formatted to expand as far as needed by author.)

Background: The drug substance is umeclidinium bromide, which is a long acting muscarinic antagonist (LAMA) to be used for maintenance treatment of Chronic Obstructive Pulmonary Disease (COPD). The device is the Ellipta™, which, based on the trademark, is the same device that is also used for the drug products of the approved N204275 (Breo Ellipta) and for N203975 (b) (4) Ellipta, currently under review).[1] The Ellipta™ device can contain two separate blister strips of pre-metered formulations, but for N205382, only a single blister strip is being used for the commercial presentation of the drug product.

The application references DMF 26339 for CMC information for the umeclidinium bromide, although the NDA contains the specification applied to the drug substance (b) (4) and associated justification.

The drug product is a pre-metered inhalation powder that includes a gray plastic inhaler,

[1] From the QOS introduction: "Several of the sections are the same/similar to that submitted for Breo Ellipta (Fluticasone Furoate/Vilanterol Inhalation Powder, NDA 204275) which is currently under review. These sections include: m3.2.P.3.3. Description of Manufacturing Process and Process Controls_Reprocessing regarding the strip filling and assembly process for vilanterol, m3.2.P.4. Control of Excipients regarding the magnesium stearate excipient, m3.2.P.6. Reference Standards regarding the vilanterol reference standards and m3.2.P.7. Container Closure."

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with a light green mouthpiece cover, as well as a dose counter. The pre-metered drug formulation is contained in a continuous blister strip of either 30 or 7 dosage units. The filled device is protected with a foil (b) (4) tray with lid, that also contains a pre-hydrated silica gel desiccant unit. Each pre-metered blister contains 62.5 mcg of umecledinium (as bromide salt). The drug product formulation is shown below:

Start of Applicant Material

Table 1 Composition for Umeclidinium Inhalation Powder 62.5 Microgram

Component	Quantity per 12.5 mg Blister[2]	Function	Reference to Standard
Umeclidinium bromide micronised	74.2 mcg[3]	Active	GlaxoSmithKline[1]
Magnesium Stearate	75 mcg	(b) (4)	JP, Ph. Eur and USP/NF[4]
Lactose Monohydrate	to 12.5 mg		JP, Ph. Eur and USP/NF[4]

Note:
mcg: microgram
1. Details of the specification of the active ingredient are provided in DMF 26339, S.4.1. Specification.
2. A manufacturing overage of up to (b) (4) of the blend may be included.
3. 74.2 micrograms of umeclidinium bromide is equivalent to 62.5 micrograms of umeclidinium ((b) (4) . (b) (4) (b) (4)
4. Excipients comply with JP, Ph. Eur and USP/NF and additional tests to ensure the quality for inhaled use. Details of the specification are provided in P.4.1.- 4.4. Control of Excipients_Lactose Monohydrate, Section 1 and P.4.1.- 4.4. Control of Excipients_Magnesium Stearate, Section 1.

End of Applicant Material

The inhaler device used for the drug product is shown (exploded view) in the figure reproduced below.

Start of Applicant Material

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Figure 7 Exploded View of the Inhaler Showing all Individual Components and Blister Strip

(b) (4)

End of Applicant Material

The applicant claims to have used Quality by Design principles in the development of their drug product, but little or no regulatory flexibility is being sought relative to previously approved inhalation powder drug products.

Critical Issues and Complexities:

- At the EOP2 meeting for the umeclidinium/vilanterol (U/V) combination product, the applicant had indicated that the aerodynamic particle size distribution (APSD) acceptance criteria for the U/V and the umeclidinium monotherapy drug product may differ (see question 10 in meeting minutes of 24-OCT-2010). The acceptance criteria for umeclidinium APSD for N203975 and N205382 differ for (b) (4) respectively). Depending on the magnitude of the differences in the associated data, the reviewer may need to inform the clinical team.

- Error's made by an analyst for several years in the testing for foreign particulate matter have resulted in the invalidation of some of the drug product stability data, which is captured in footnotes in the stability data tables. Data from later time

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points are substituted in some cases. The applicant claims that the "data generated are satisfactory and the conclusions drawn from FP Matter data are unaltered."

- There have been some changes made to the inhaler from Phase III to that intended for commercial marketing. These are outlined and said to be supported with data in P.2.4.

- As per footnote k for the drug product specification, the applicant proposes a [redacted] (b) (4) for the [redacted] (b) (4) determinations of aerodynamic particle size distribution (APSD).

- The applicant proposes a parametric tolerance interval test (PTIT) approach for the assessment of content uniformity of the emitted dose (i.e., delivered dose uniformity or DDU). The biometrics team may need to be consulted if this approach differs from that with which we approved under N204275.

- The specification requirement for microbiology quality for the drug product is unique in that it proposes a two-tiered approach that uses water activity testing for the first tier and standard microbial limits testing for the second tier.

- The specification for the drug product does not require the testing for drug-related impurities at release.

Description of Facility Related Risks or Complexities (i.e. foreign sites, large number of sites involved, etc.)
See EES for complete list of facilities related to this application.

Biopharmaceutics Filing Review:
Summary, Critical Issues and Complexities

(This section can expand as far as needed by author.)

Note: A separate filing review will be provided by the biopharmaceutics team.

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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?	☐	☐		All pages examined for production of this IQA were legible
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X	☐	☐	The adequacy of the provided data will be determined during review

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	☐	☐	See module 1.1.2 of Sequence # 0000
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	

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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	☐	The applicant did not indicate in form 356h that the umeclidinium bromide manufacturing information is referenced to DMF 26339 (this should be noted by the PM in the EER submitted in the EES)
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	☐	☐	

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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	☐	☐	

* 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	☐	☐	It is left to the reviewer to decide whether or not supportive information or data is needed to support the request for categorical exclusion under 21 CFR 25.31(b); Applicant also claims that they know of no extraordinary circumstances regarding the EA.

D. MASTER FILES (DMF/MAF)					
	Parameter	**Yes**	**No**	**N/A**	**Comment**

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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.*

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?	☐	☐	☐	Yes, by reference to DMF 26339
14.	Does the section contain identification and controls of critical steps and intermediates of the DS (in process parameters?	☐	☐	☐	See comment for 13 above
15.	Does the section contain information on impurities?	☐	☐	☐	See comment for 13 above
16.	Does the section contain information regarding the characterization of the DS?	☐	☐	☐	See comment for 13 above
17.	Does the section contain controls for the DS?	☐	☐	☐	See comment for 13 above; the NDA contains the specification sheet for the drug substance
18.	Has stability data and analysis been provided for the drug substance?	☐	☐	☐	See comment for 13 above
19.	Does the application contain Quality by Design (QbD) information regarding the DS?	☐	☐	☐	See comment for 13 above
20.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?	☐	X	☐	
21.	Does the section contain container and closure information?	☐	☐	☐	See comment for 13 above

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F. DRUG PRODUCT (DP)					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
22.	Does the section contain quality controls of excipients?	X	☐	☐	
23.	Does the section contain information on composition?	X	☐	☐	
24.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X	☐	☐	
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	☐	☐	Refer to P.3.4 for control of critical steps; there are no intermediate products associated with the drug product manufacture
26.	Is there a batch production record and a proposed master batch record?	X	☐	☐	
27.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	☐	X	☐	The P.2.2 formulation development section does include a summary of earlier formulations that contained (b) (4) Safety assessment led to a change from (b) (4) The formulation used in the phase III clinical studies and the primary stability studies is the same as that proposed for commercial distribution. Note that the applicant has made changes to the inhaler and protective packaging, however (see P.2.4).
28.	Have any biowaivers been requested?	☐	X	☐	
29.	Does the section contain description of to-be-marketed container/closure system and presentations?	X	☐	☐	Also see the review of DMF (b) (4) for the (b) (4)

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30.	Does the section contain controls of the final drug product?	X	☐	☐	The reviewer can assess the drug product control relative to what was approved for N204275 to assure consistency, particularly for unique features (e.g., PTIT for DDU, APSD (b) (4) proposal, two tier/method microbiology testing, no impurities testing at release)
31.	Has stability data and analysis been provided to support the requested expiration date?	X	☐	☐	Fifteen months of long term (25°C/60%RH) stability data provided for three batches manufactured at the commercial site (b) (4) using a "representative commercial process." The scale was (b) (4) kg (said to be "typical"), but packaging was said to be pilot scale. Statistical analysis (assay and APSD grouping data) are provided to support the proposed expiry of 24 months. Twelve months of 30°C/75%RH data are also provided, along with 6 months of 40°C/75%RH data. Three months of 25°C/75%RH in-use stability data are provided on product stored first for 6 and 9 months for 25°C/60%RH (a 6-week in-use period is proposed). Note that not all test parameters are examined at each stability time-point.
32.	Does the application contain Quality by Design (QbD) information regarding the DP?	X	☐	☐	The applicant's QbD approach is outlined in P.2.1. The only "regulatory flexibility" that is observed is the absence of testing of the drug product for impurities at release (same approach as for approved N204275). QbD principles were also applied in the method development (see P.5.3). No design spaces are proposed.
33.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	☐	X	☐	

G. METHODS VALIDATION (MV)					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
34.	Is there a methods validation package?	X	☐	☐	

H. MICROBIOLOGY					
	Parameter	**Yes**	**No**	**N/A**	**Comment**

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35.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?	☐	☐	X	Product is not sterile

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	☐	☐	
38.	Does section contain tradename and established name?	X	☐	☐	

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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.	☐	☐	X	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	☐	Describe potential review issues here or on additional sheets

REVIEW AND APPROVAL

This document will be signed in DARRTS by the following:

CMC Lead or CMC Reviewer
Branch Chief

{See appended electronic signature page}

Reference ID: 3316193

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

/s/

CRAIG M BERTHA
05/30/2013

PRASAD PERI
05/31/2013
I concur