

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202450Orig1s000

CHEMISTRY REVIEW(S)

NDA 202450

Tudorza Pressair (Acclidinium Bromide Inhalation Powder)

Forest Laboratories, Inc.

Yong Hu, Ph.D.

**Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment**

For

Division of Pulmonary, Allergy and Rheumatology Products

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Chemistry Review Data Sheet

1. NDA: 202450
2. REVIEW #: 2
3. REVIEW DATE: 15-May-2012
4. REVIEWER: Yong Hu, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original submission	23-Jun-2011
Amendment (Response to CMC comments in the 74-day letter)	23-Sep-2011
Amendment (Drug product stability update with 18-month data)	19-Oct-2011

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Quality/Response to Information Request	11-May-2012
Quality/Response to Information Request	20-Mar-2012
Quality/Response to Information Request	13-Mar-2012
Quality/Response to Information Request	23-Feb-2012

7. NAME & ADDRESS OF APPLICANT:

Name: Forest Laboratories, Inc
Address: Harborside Financial Center, Plaza V, Suite 1900,
Jersey City, NJ 07311
Representative: Amjad M. Iqbal, Pharm. D.,
Associate Director, Regulatory Affairs
Telephone: 201-386-2117

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Tudorza Pressair
- b) Non-Proprietary Name (USAN): Aclidinium bromide inhalation powder
- c) Code Name/# (ONDC only): LAS 34273, 14115700, LAS W-330, LASW330
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

505 b(1)

10. PHARMACOL. CATEGORY:

Muscarinic receptor antagonist that is highly selective for the M3 receptor

11. DOSAGE FORM:

Inhalation powder; Device-metered dry powder inhaler (DPI).

12. STRENGTH/POTENCY:

400 µg (Metered dose); 375 µg (Delivered dose)

13. ROUTE OF ADMINISTRATION:

Oral inhalation

14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

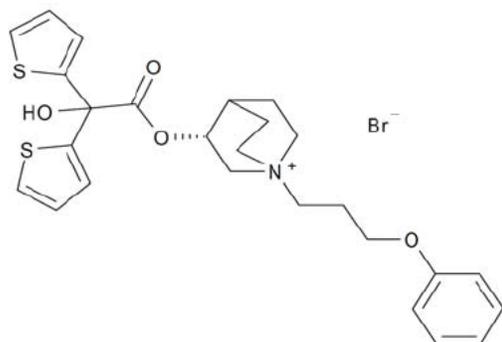
Not a SPOTS product

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

(1) 1-Azoniabicyclo[2.2.2]octane, 3-[(hydroxydi-2-thienylacetyl)oxy]-1-(3-phenoxypropyl)-, bromide, (3R)-;

(2) (3R)-3-[[Hydroxydi(thiophen-2-yl)acetyl]oxy]-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide.

Chemistry Review Data Sheet



$C_{26}H_{30}NO_4S_2Br$. 564.56.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCE D	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Acridinium bromide	1	Adequate	04-Jan-2012	
	III	(b) (4)		1	Adequate	26-Mar-2012	
	IV	(b) (4)		4	N/A	N/A	

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 is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	68,653	The IND for acridinium bromide.

Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not requested.		
EES	Acceptable.	18-Apr-2012	D. Smith
Pharm/Tox	<p>The impurity limits for (b) (4) in the drug substance specification are qualified. The below five impurities in the drug substance with structural alerts for genotoxicity are considered qualified. Three of these impurities (b) (4) are considered qualified based upon negative Ames test results and control at NMT (b) (4) in the drug substance. The remaining two impurities (b) (4) which are both positive in bacterial mutagenicity tests, are considered qualified based upon control at (b) (4) µg/day for the summed amount of these two impurities (since both are (b) (4)). The impurities (b) (4) are considered qualified. The specification limits for (b) (4) are considered acceptable.</p>	Consult review signed-off in DARRTS on 13-Mar-2012	Grace Lee
Biopharm	Not applicable.		
LNC	Not requested.		
Methods Validation	The FDA lab has completed its evaluation of the dose content uniformity and aerodynamic particle size distribution methods. Minor modifications were recommended. The applicant has agreed to the modifications (see this review).	30-Apr-2012	Xiaofei Liu; James Allgire
OPDRA	Not requested.		
EA	Acceptable.	16-Feb-2012	Yong Hu
Microbiology	Acceptable.	06-Dec-2011	Jessica Cole

The Chemistry Review for NDA 202450

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The NDA is recommended for approval from CMC perspective.

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)

The drug substance is micronized acridinium bromide. The compound is a (b) (4) according to the polymorph screening results. It is manufactured by (b) (4) and micronized by (b) (4). The detailed information for the drug substance is provided by cross-referencing the DMF (b) (4). The manufacturing and testing facilities are deemed acceptable by the Office of Compliance.

One of the starting materials, (b) (4) is potentially genotoxic. One of the impurities in (b) (4) can lead to another potentially genotoxic impurity, (b) (4) in the final drug substance. The control strategy for the genotoxic impurities involves the DMF holder's commitment to the current synthesis route for the starting material by using the selected suppliers, control of the impurities in the starting material, and final drug substance specification to control the amount of the starting material as an impurity in the drug substance. The DMF holder has provided a commitment that, if the suppliers for the starting material (b) (4) change in the future, the holder will re-evaluate the presence of genotoxic impurities in the drug substance. Most of the drug substance batches used in the pivotal clinical studies were manufactured with the proposed commercial process at the full commercial scale in the commercial site. The drug substance is stored (b) (4).

The re-test period is (b) (4).

The drug product is a non-refillable, breath-actuated, device-metered, multi-dose dry powder inhaler with a green protective cap, green dosage key, and white body. The device is called Almirall inhaler (manufactured by (b) (4) and has evolved from the (b) (4) a device approved for several medicinal products in Europe. The inhalation

Executive Summary Section

powder consists of the drug substance and α -lactose monohydrate and is stored in a cartridge inside the inhaler. Each actuation meters 13 mg of the powder containing 400 μ g of acclidinium bromide and delivers 375 μ g of acclidinium bromide from the mouthpiece. Each inhaler delivers a minimum of 60 doses (b) (4) before the device locks out with the majority of inhalers locking out at the (b) (4) dose. Based on the characterization data in the NDA, the last dose before device lockout showed similar dose content and aerodynamic particle size distribution (APSD) as the initial 60 doses. Despite this, the patients should be instructed to start a new inhaler after 60 doses as the routine quality control for dose content uniformity and APSD over the life of the inhalers will not be conducted using the doses beyond the 60th dose. In addition, the characterization data also showed that a full dose can be delivered with a minimum of air flow rate of 35 L/min.

The drug product is manufactured by Forest Laboratories in Ireland. The phase 3 pivotal clinical studies used the drug product batches manufactured with the commercial manufacturing process at the full commercial scale at the commercial site. All the drug product manufacturing and testing facilities have been deemed acceptable by the Office of Compliance.

The inhaler is sealed in an aluminum pouch and packaged in a cardboard carton. A shelf-life of 24 months is acceptable for the drug product with a labeled storage statement of “Store at 25 °C (77 °F); excursions permitted from 15° to 30 °C (59° – 86 °F) [See USP Controlled Room Temperature]”.

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

Acclidinium bromide is a long acting antimuscarinic agent indicated for the long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD). The drug product is for oral inhalation only. The recommended dosage is one inhalation (400 μ g) twice daily.

Typical to all dry powder inhalers, the patient’s inhalation provides the energy to aerosolize the formulation within the device. The inhaler’s integrated dose indicator is designed to illustrate how many doses remain with markings of 60, 50, 40, 30, 20, 10, and 0. The device is designed to lock out after a minimum of 60 doses (b) (4) with the data from 18 inhaler batches showing that most devices locked out between (b) (4) doses. The patient should start a new inhaler when the marking “0” with a red background fully shows on the right side of the dose indicator window, indicating that 60 doses have been taken. The inhaler also has a colored control window that changes from red to green when the inhaler is ready for inhalation and changes from green to red when the dose is delivered correctly and is accompanied by an audible ‘click’ sound.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has provided adequate Chemistry, Manufacturing, and Controls information in the original NDA and through the responses to CMC information requests. The overall

Executive Summary Section

recommendation from the Office of Compliance regarding the manufacturing and testing facilities is “Acceptable”.

III. Administrative**A. Reviewer’s Signature**

See DARRTS

B. Endorsement Block

See DARRTS.

C. CC Block

See DARRTS.

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/s/

YONG HU
05/25/2012

PRASAD PERI
05/28/2012
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION REPORT SUMMARY

TO: Yong Hu, CMC Reviewer
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: Yong.Hu@fda.hhs.gov
Phone: (301)-796-5031
Fax: (301)-

FROM: FDA
Division of Pharmaceutical Analysis
James Allgire, Team Leader
Suite 1002
1114 Market Street
St. Louis, MO 63101
Phone: (314) 539-3813

Through: Benjamin J. Westenberger, Deputy Director
Phone: (314) 539-3869

SUBJECT: Methods Validation Report Summary

Application Number: NDA 202-450

Name of Product: Acclidinium bromide dry powder inhaler, 400 mcg

Applicant: Forrest laboratories

Applicant's Contact Person: Amjad M Iqbal

Address: Harborside Financial Center, Plaza V, Suite 1900, Jersey City, NJ 07311

Telephone: 201-386-2117 Fax: 631-858-7921

Date Methods Validation Consult Request Form Received by DPA: 12/08/11

Date Methods Validation Package Received by DPA: 12/08/11

Date Samples Received by DPA: 1/11/12

Date Analytical Completed by DPA: 4/27/12

Laboratory Classification: **1.** Methods are acceptable for control and regulatory purposes.
2. Methods are acceptable with modifications (as stated in accompanying report).
3. Methods are unacceptable for regulatory purposes.

Comments:

Cover memo and summary of results are attached.



Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
St. Louis, MO 63101
Tel. (314) 539-3794

Date: April 20, 2012
To: Yong Hu, CMC Reviewer
Alan Schroeder, CMC Lead
Through: B. J. Westenberger, Deputy Director, Division of Pharmaceutical Analysis, (HFD-920)
From: Xiaofei Liu, Chemist (HFD-920)
Subject: Methods Validation for NDA 202-450
Acclidinum bromide dry powder inhaler, 400 mcg
Forrest Laboratories

The following methods were evaluated and are acceptable for quality control and regulatory purposes with modifications:

1. PRD-TM-ANL-00484 Dose Content Uniformity Determination for Acclidinum Bromide (LAS 34273) contained in LAS 34273 Powder for Inhalation, 400 µg/Dose by HPLC
2. PRD-TM-ANL-00482 Aerodynamic Particle Assessment of Acclidinum Bromide (LAS 34273) contained in LAS 34273 Powder for Inhalation, 400 µg/Dose by HPLC

The Division of Pharmaceutical Analysis (DPA) considers the following modification essential to the methods:

1. PRD-TM-ANL-00484 Dose Content Uniformity Determination for Acclidinum Bromide (LAS 34273) contained in LAS 34273 Powder for Inhalation, 400 µg/Dose by HPLC
 - On page 7, the method states [REDACTED] (b) (4)
 - On page 7, the method states [REDACTED] (b) (4)

The Division of Pharmaceutical Analysis (DPA) has the following comments pertaining to these methods:

2. PRD-TM-ANL-00482 Aerodynamic Particle Assessment of Acclidinum Bromide (LAS 34273) contained in LAS 34273 Powder for Inhalation, 400 µg/Dose by HPLC
 - Aerodynamic Particle Size Distribution (ASPD) of Acclidinum Bromide (LAS 34273) is evaluated using [REDACTED] (b) (4)
 - On page 11, the method states MMAD is the “Mass Mean Aerodynamic Diameter”, but MMAD is actually the “Mass Median Aerodynamic Diameter.”

- Method PRD-TM-ANL-00484: Dose Content Uniformity Determination for Acclidinium Bromide (LAS 34273) contained in LAS 34273 Powder for Inhalation, 400 µg/Dose by HPLC

Results

	Dose 1	Dose 30	Dose 60	Average
Individual Recovered Amount(ug)	(b) (4)			
% Avg. Dose Content Uniformity				
% Nominal Dose				

(b) (4)

	Dose 1	Dose 30	Dose 60	Average	Specification
Individual Recovered Amount (µg)	(b) (4)				
% Avg. Dose Content Uniformity					
% Nominal Dose					

- Method PRD-TM-ANL-00482: Aerodynamic Particle Assessment of Acclidinium Bromide (LAS 34273) contained in LAS 34273 Powder for Inhalation, 400 µg/Dose by HPLC

Results

	Amt per actuation (µg)			Specification
	Dose 1	Dose 30	Dose 60	
Sum	(b) (4)			(b) (4)
Sum				
Sum				
Sum				
Total (ug)				
Average (ug)				
Total Sum (% of Average)				
Fine Particle Dose				
MMAD (um)				

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/s/

JAMES F ALLGIRE
04/27/2012

BENJAMIN J WESTENBERGER
04/30/2012

NDA 202450

Tudorza Pressair (Acclidinium Bromide Inhalation Powder)

Forest Laboratories, Inc.

Yong Hu, Ph.D.

**Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment**

For

Division of Pulmonary, Allergy and Rheumatology Products

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Chemistry Review Data Sheet

1. NDA: 202450
2. REVIEW #: 1
3. REVIEW DATE: 24-Feb-2012
4. REVIEWER: Yong Hu, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

N/A

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original submission

23-Jun-2011

Amendment (Response to CMC comments in the
74-day letter

23-Sep-2011

Amendment (Drug product stability update with
18-month data)

19-Oct-2011

7. NAME & ADDRESS OF APPLICANT:

Name: Forest Laboratories, Inc
Address: Harborside Financial Center, Plaza V, Suite 1900,
Jersey City, NJ 07311
Representative: Amjad M. Iqbal, Pharm. D.,
Associate Director, Regulatory Affairs
Telephone: 201-386-2117

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Tudorza Pressair

Chemistry Review Data Sheet

- b) Non-Proprietary Name (USAN): Acclidinium bromide inhalation powder
c) Code Name/# (ONDC only): LAS 34273, 14115700, LAS W-330, LASW330
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 1
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

505 b(1)

10. PHARMACOL. CATEGORY:

Muscarinic receptor antagonist that is highly selective for the M3 receptor

11. DOSAGE FORM:

Inhalation powder; Device-metered dry powder inhaler (DPI).

12. STRENGTH/POTENCY:

400 µg (metered dose); 375 µg (Delivered dose)

13. ROUTE OF ADMINISTRATION:

Oral inhalation

14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

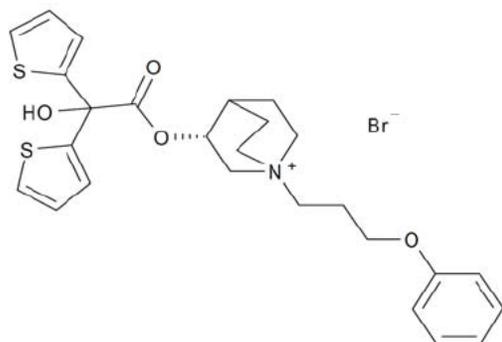
SPOTS product – Form Completed

Not a SPOTS product

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

- (1) 1-Azoniabicyclo[2.2.2]octane, 3-[(hydroxydi-2-thienylacetyl)oxy]-1-(3-phenoxypropyl)-, bromide, (3R)-;
(2) (3R)-3-{[Hydroxydi(thiophen-2-yl)acetyl]oxy}-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide.

Chemistry Review Data Sheet



$C_{26}H_{30}NO_4S_2Br$. 564.56.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCE D	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Acridinium bromide	1	Adequate	04-Jan-2012	
	III	(b) (4)	(b) (4)	7	Inadequate	N/A	Deficiency in specification for (b) (4) studies of device components
	IV	(b) (4)	(b) (4)	4	N/A	N/A	

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 is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

Chemistry Review Data Sheet

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	68,653	The IND for aclidinium bromide.

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not requested.		
EES	Pending.		
Pharm/Tox	The impurity limits in the drug substance specification are qualified. The total amount of genotoxic impurities in the drug substance, (b) (4) should not exceed (b) (4) µg/day.	28-Nov-2011	Grace Lee
Biopharm	Not applicable.		
LNC	Not requested.		
Methods Validation	The FDA lab is evaluating for the dose content uniformity and aerodynamic particle size distribution methods for the drug product and the results are pending. Completion of this testing is not required prior to action on the NDA.		
OPDRA	Not requested.		
EA	Acceptable.	16-Feb-2012	Yong Hu
Microbiology	Acceptable.	06-Dec-2011	Jessica Cole

The Chemistry Review for NDA 202450

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The NDA is approvable. The final recommendation is pending because this reviewer is waiting for the following information.

1. The applicant's response to CMC information request (see the end of this review);
2. The overall recommendation on the facilities from the Office of Compliance;
3. Revised specifications for (b) (4) for the inhaler components by the holder of DMF (b) (4);

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

None at this time.

II. Summary of Chemistry Assessments

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

The drug substance is micronized acridinium bromide. The compound is (b) (4) according to the polymorph screening results. It is manufactured by (b) (4) and micronized by (b) (4). The detailed information for the drug substance is provided by cross-referencing the DMF (b) (4). The overall recommendation in the Establishment Evaluation System (EES) for the facilities is pending.

One of the starting materials, (b) (4) is potentially genotoxic. One of the impurities in (b) (4) can lead to another potentially genotoxic impurity, (b) (4), in the final drug substance. The control strategy for the genotoxic impurities involves the DMF holder's commitment to the current synthesis route for the starting material by using the selected suppliers, control of the impurities in the starting material, and final drug substance specification to control the amount of the starting material as an impurity in the drug substance. The DMF holder has provided a commitment that, if the suppliers for the starting material (b) (4) change in the future, the holder will re-evaluate the presence of genotoxic impurities in the drug substance. Most of the drug substance batches used in the pivotal clinical studies were manufactured with the proposed commercial process at the full commercial scale in the commercial site. The drug substance is stored (b) (4).

The re-test period is (b) (4).

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The drug product is a non-refillable, breath-actuated, device-metered, multi-dose dry powder inhaler with a green protective cap, green dosage key, and white body. The device is called Almirall inhaler (manufactured by (b) (4)) and has evolved from the (b) (4), a device approved for several medicinal products in Europe. The inhalation powder consists of the drug substance and α -lactose monohydrate and is stored in a cartridge inside the inhaler. Each actuation meters 13 mg of the powder containing 400 μ g of acclidinium bromide and delivers 375 μ g of acclidinium bromide from the mouthpiece. Each inhaler delivers a minimum of 60 doses (b) (4) before the device locks out. Based on the characterization data in the NDA, the full dose can be delivered with a minimum of (b) (4) flow rate. The inhaler is sealed in an aluminum pouch and packaged in a cardboard carton.

The drug product is manufactured by Forest Laboratories in Ireland. The phase 3 pivotal clinical studies used the drug product batches manufactured with the commercial manufacturing process at the full commercial scale at the commercial site. The overall recommendation in the Establishment Evaluation System (EES) for the facilities is pending.

A shelf-life of 24 months is proposed for the drug product with a labeled storage statement of “Store at 25 °C (77 °F): excursions permitted from 15° to 30 °C (59° – 86 °F) [See USP Controlled Room Temperature]”.

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

Acclidinium bromide is a long acting antimuscarinic agent indicated for the long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD). The drug product is for inhalation only. The recommended dosage is one inhalation (400 μ g) twice daily.

Typical to all dry powder inhalers, the patient’s inhalation provides the energy to aerosolize the formulation within the device. The inhaler’s integrated dose indicator is designed to illustrate how many doses remain with markings of 60, 50, 40, 30, 20, 10, and 0, and it locks out after a variable doses but a minimum of 60 doses. A locked inhaler will not deliver any acclidinium bromide powder and should be discarded. The inhaler also has a colored control window that changes from red to green when the inhaler is ready for inhalation and changes from green to red when the dose is delivered correctly and is accompanied by an audible ‘click’ sound. The Patient Use Instructions state that (b) (4)

C. Basis for Approvability or Not-Approval Recommendation

The drug product specifications for dose content uniformity (DCU) and aerodynamic particle size distribution (APSD) need some revisions as outlined in the information request at the end of this review. The overall recommendation from the Office of Compliance regarding the facilities

Executive Summary Section

is pending. The FDA lab's evaluation of the two analytical methods (for DCU and APSD) is also pending.

III. Administrative**A. Reviewer's Signature**

See DARRTS

B. Endorsement Block

See DARRTS.

C. CC Block

See DARRTS.

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/s/

YONG HU
02/24/2012

The Deficiencies/Information request have been communicated to the applicant. No need to send again.

PRASAD PERI
02/24/2012
I concur

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION CONSULT REQUEST FORM

TO: FDA
Division of Pharmaceutical Analysis
Attn: Benjamin (Nick) Westenberger
Suite 1002
1114 Market Street
St. Louis, MO 63101

FROM: Yong Hu, CMC Reviewer
Alan Schroeder, CMC Lead
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: yong.hu@fda.hhs.gov
Phone: (301)-796-5031
Fax.: (301)-

Through: Prasad Peri, Branch Chief
Phone: (301)-796-1730

and

Jeannie David, ONDQA Methods Validation Project Manager
Phone: 301-796-4247

SUBJECT: Methods Validation Request

Application Number: NDA 202-450

Name of Product: Acridinium bromide dry powder inhaler, 400 mcg

Applicant: Forrest Laboratories

Applicant's Contact Person: Amjad M. Iqbal

Address: Harborside Financial Center, Plaza V, Suite 1900, Jersey City, NJ 07311

Telephone: 201-386-2117 Fax: 631-858-7921

Date NDA Received by CDER: **6/23/11**

Submission Classification/Chemical Class: Type 1

Date of Amendment(s) containing the MVP: **9/23/2011**

Special Handling Required: No

DATE of Request: **December 6, 2011**

DEA Class: N/A

Requested Completion Date: **2/23/2012**

Format of Methods Validation Package (MVP)

PDUFA User Fee Goal Date: **4/23/2012**

Paper Electronic Mixed

We request suitability evaluation of the proposed manufacturing controls/analytical methods as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request*. Upon receipt of the samples, perform the tests indicated in Item 3 of the attached *Methods Validation Request* as described in the NDA. We request your report to be submitted in DARRTS promptly upon completion, but no later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager of the date that the validation process begins. If the requested completion date cannot be met, please promptly notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying *Methods Validation Report Summary*). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by the director via DARRTS. The ONDQA CMC Reviewer, ONDQA Methods Validation Project Manager, and ONDQA CMC Lead/Branch Chief should be included as cc: recipients for this document.

All information relative to this application is to be held confidential as required by 21 CFR 314.430.

MVP Reference #	METHODS VALIDATION REQUEST			NDA # 202-450
⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT				
ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION		
NA. Applicant is ready to submit samples upon request as indicated in their response to 74-day letter.				
⇒ ITEM 2: Contents of Attached Methods Validation Package				Volume/Page Number(s)
Statement of Composition of Finished Dosage Form(s)				3.2.P.1
Specifications/Methods for New Drug Substance(s)				3.2.S.4.1
Specifications/Methods for Finished Dosage Form(s)				3.2.P.5.1
Supporting Data for Accuracy, Specificity, etc.				3.2.P.5.3
Applicant's Test Results on NDS and Dosage Forms				3.2.P.5.4; 3.2.P.2
Other:				
⇒ ITEM 3: REQUESTED DETERMINATIONS Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.				
Method ID	Method Title	Volume/Page	MV Request Category (see attached)	Comments
PRD-TM-ANL-00482	Aerodynamic Particle Assessment of Acridinium Bromide (LAS 34273) Contained in LAS 34273 Powder for Inhalation, 400 µg/Dose (b)(4) 60 Dose Filled Cartridges)(by HPLC)	3.2.P.5.2	0 2	The compound is an NME and the method is a critical one for the dry powder inhaler.
PRD-TM-ANL-00484	Dose Content Uniformity Determination for Acridinium Bromide (LAS 34273) Contained in LAS 34273 Powder for Inhalation, 400 µg/Dose (b)(4) 60 Dose Filled Cartridges) (by HPLC)	3.2.P.5.2	0 2	The compound is an NME and the method is a critical one for the dry powder inhaler.

Additional Comments:

Methods Validation Request Criteria

MV Request Category	Description
0	New Molecular Entity (NME) application, New Dosage Form or New Delivery System
1	Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)
2	Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms)
3	Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)
4	Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)
5	Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method)

6	Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation)
7	Methods that are subject to a “for cause” reason

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

/s/

YONG HU
12/08/2011

PRASAD PERI
12/08/2011

JEANNIE C DAVID
12/08/2011
ONDQA Methods Validation Project Manager

**ONDQA Review for
OND Division of Pulmonary Allergy and Rheumatology Products
Initial Quality Assessment and Filing Review
Date: August 26, 2011**

NDA: 202450

Product Name: no proprietary name yet ((b) (4) proposed)

Applicant: Forest Laboratories, Inc.

Stamp Date: June 23, 2011

PDUFA Date: April 23, 2012

ONDQA 5 month date: September 23, 2011

Proposed Proprietary Name: (b) (4)

Established Name: acclidinium bromide

Dosage form and strength: powder, metered

Route of Administration: respiratory (inhalation)

Indications: CMC Lead (acting): Alan C. Schroeder, Ph.D. /DNDQA III/ONDQA

Filability recommendation: Fileable.

Review team recommendation: Single primary reviewer (Yong Hu, Ph.D.)

Recommended briefing level: Office Level (NME)

Time goals:

- Initial Quality Assessment in DFS: August 22, 2011
- Filing decision “Day 60”: August 22, 2011
- Filing review issues “Day 74”: September 5, 2011
- **Chemistry Review (DR/IR) letter:** by November 23, 2011
- Mid-cycle meeting “Month 5”: November 28, 2011
- Wrap Up meeting: March 12, 2012
- **Final Chemistry Review “Month 8” in DFS:** February 23, 2012
- PDUFA Goal Date: April 23, 2012

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharm	NA
CDRH	Not necessary. The device has no electronic components.
EA	To be assessed by Primary Reviewer
EES	EER sent to Office of Compliance on July 14, 2011
DMETS	Labeling consult request will be sent as part of DPARP’s request.
Methods Validation	Methods validation for one or more non-compendial methods will be requested of FDA laboratories once the applicant submits a MV package (to be requested with filing comments) since this drug is an NME.
Microbiology	A consult is recommended for drug product microbial limits testing; however, USP <61>, <62> and <1111> are referenced , with no actual method description provided. It should be determined first whether the USP description for microbial limits testing is adequate, or if the method used should be fully

CONSULTS/ CMC RELATED REVIEWS	COMMENT
	described. The justification for lack of microbial limits testing of the drug substance should be evaluated.
Pharm/Tox	DS and DP impurities/degradants/leachables to be evaluated for safety.

Notes:

Background:

The proposed indication is as follows: “aclidinium bromide 400ug BID for the long-term maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema.”

The following information was provided in the Quality Overall Summary (in Module 2).

“Aclidinium bromide Inhalation Powder, 400 µg, is a white or almost white inhalation powder and is presented in the Almirall Inhaler, which is a device metered multi-dose dry powder inhaler (DPI). Each actuation of the inhaler delivers approximately 375 µg of aclidinium bromide from the mouthpiece (based on in vitro testing at 60 L/min for 2 sec), corresponding to a metered dose of approximately 400 µg of aclidinium bromide. Each metered dose is approximately 13 mg of which 400 µg is aclidinium bromide and the remainder is α-lactose monohydrate. . .Aclidinium bromide inhalation powder is (b) (4) micronized aclidinium bromide (active substance) and α-lactose monohydrate carrier (b) (4). The manufacturing process for the aclidinium bromide inhalation powder consists of (b) (4)

“The Almirall inhaler is a white device-metered inhaler with a green protective cap, green dosage key, fixed mouthpiece and slide cover with a 60-dose counter ring cartridge that contains the inhalation powder. The inhaler is enclosed in an aluminum pouch. The pouch is heat sealed and packaged in an outer carton.” It is stated that the Almirall inhaler is an improved version of the (b) (4). The product is disposable/non-refillable once the labeled number of doses have been delivered. The Almirall inhaler contains a lock-out system that delivers “at least 60 doses before the device locks.” Differences between the Almirall inhalaer and the (b) (4) are discussed in section 2.3.P.2.4. [CMC data for the device are referenced to DMF (b) (4)]

Drug substance

This drug substance is a “long-acting antimuscarinic agent co-developed by Almirall and Forest for the treatment of patients with COPD, including chronic bronchitis and emphysema. Reference is made to IND 68,653 for aclidinium bromide...”

Drug substance information (aclidinium bromide micronized drug substance) is referenced to DMF (b) (4). Assessment of this DMF is not included in this IQA for confidentiality reasons. This DMF was previously reviewed by Dr. Prasad Peri on 3/15/2004 and found adequate for an IND. This DMF was completely updated (7 volumes) on 4/29/11 (date of submission). The following drug substance information in this review was provided by the applicant in the NDA.

“NOMENCLATURE

International Non-Proprietary Name (INN) and United States Approved Name (USAN):

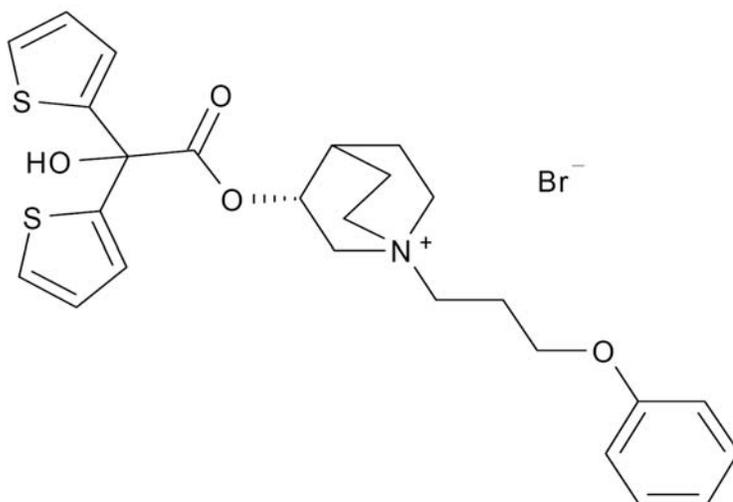
Aclidinium bromide

Chemical Names:

IUPAC: (3R)-3-[(hydroxy)di(thiophen-2-yl)acetyloxy]-1-(3-phenoxypropyl)-1λ⁵-azabicyclo[2.2.2]octan-1-ylum bromide

1-Azoniabicyclo[2.2.2]octane, 3-[(hydroxydi-2-thienylacetyl)oxy]-1-(3-phenoxypropyl)-, bromide, (3R)-“

“The drug substance has one chiral center. Aclidinium bromide has a single stereoisomer with the (3R) configuration.”

Structural Formula:

Comment: for a separate supplier, NDA needs drug substance specifications so they can periodically check the COAs.

The following information is from section 2.3.S and 2.3.P of the NDA:

“The physicochemical characteristics of the micronized drug substance that may influence the quality of the inhalation powder drug product have been evaluated. The studies include the evaluation of solid state characteristics such as particle size distribution (PSD), amorphous content, density, specific surface area, particle shape, rugosity and surface roughness (texture). These physicochemical characteristics can potentially affect the adhesion and cohesion forces among drug substance particles or between drug substance and excipient particles which eventually determine separation of the powder components, delivery to the lungs and deposition in the airways. These key characteristics are discussed in detail in Section 3.2.P.2.1.” (pg. 8 of 2.3.P).

The drug substance is micronized (b) (4)

(b) (4) The applicant notes a strong correlation exists between the particle size distribution of the micronized acclidinium bromide and the fine particle dose of the drug product. Various solid state properties have been studied (pg. 9, section 2.3.P). (b) (4)

“Amorphous content is recognized as a Critical Quality Attribute (CQA) and is quantified by (b) (4) Type II DMF (b) (4) Other “key physicochemical characteristics” of the drug substance are described (see pp. 8-16 of the QOS, section 2.3.P).

Comment: The reviewer should see whether adequate data are provided to justify not testing the amorphous content of the drug substance on stability.

Drug substance specifications:

(See next page)

Table 4.1-1. Specification for Acridinium bromide micronized Drug Substance

<i>Test</i>	<i>Acceptance Criteria</i>	<i>Method</i>	
Description	White or off-white powder	Visual inspection	
Melting point	224 – 229°C	Ph. Eur. 2.2.14	
Color of solution	Not more intensely colored than reference solution (b) (4)	Ph. Eur. 2.2.2, method I (50 mg/ml solution in DMSO)	
<i>Identification:</i>			
Infrared	Conforms to reference spectrum	Ph. Eur. 2.2.24, KBr disc or attenuated total reflection (ATR)	
Bromides	Positive	Ph. Eur. 2.3.1(a)	
(b) (4)	(b) (4)	In-house (b) (4)	
		Ph. Eur. 2.2.32 (d) (1 g, 105°C)	
		Ph. Eur. 2.4.14 /USP <281>	
Heavy metals	(b) (4)	USP <231>, Method II	
HPLC assay (% expressed on dry product basis)	(b) (4)	In-house HPLC	
(b) (4)			
			In-house HPLC
			In-house HPCE

Drug Substance Specifications, cont'd

Table 4.1-1. Specification for Acclidinium bromide micronized Drug Substance

<i>Test</i>	<i>Acceptance Criteria</i>	<i>Method</i>
(b) (4)	(b) (4)	In-house HPLC/SPE
Total impurities (all methods)	(b) (4)	In-house HPLC, HPCE and HPLC/SPE
(b) (4)	(b) (4)	Ph. Eur. 2.4.24, system A
(b) (4)	(b) (4)	In-house (b) (4)

Drug product



See the background section of this review for a description of the drug product.

The drug product contains a *single excipient*, α -lactose monohydrate (b) (4). Lactose is not a novel excipient for the inhalation route of administration. A (b) (4) lactose was used in this formulation of drug product. A majority of the lactose is said to have a particle size of (b) (4). Controls have been developed

to ensure (b) (4). Chemical compatibility between lactose and the drug substance are said to be indicated by ICH long term and accelerated stability studies. (b) (4)

(b) (4)

Since all batches complied with the acceptance criteria, it is proposed not to perform this test on a routine basis (Table 3.2.P.2.1.2–2). Moreover these impurities are also controlled by the measurement of the absorption between (b) (4) which will continue to be tested as required by the USP monograph for α -lactose monohydrate... The (b) (4) impurities content has been monitored throughout the development. The results of lactose batches (Table 3.2.P.2.1.2–3) demonstrate that the content of (b) (4) impurities is consistently within the specification with (b) (4) impurities below (b) (4). Since these impurities are not relevant from toxicological perspective, and present in very small quantities, (b) (4) [Section 2.3.P] [Comment: see if these rationales for removing testing of the indicated attributes are scientifically acceptable.]

Changes in the DPI device and formulation during development:

(b) (4)

“Once the exploratory development studies (pharmacokinetic profile, safety and tolerability) were completed, *full development* (starting with the dose finding study up to the current registration batches of acclidinium bromide inhalation powder) was performed with the Almirall Inhaler. The Almirall Inhaler is a multi-dose device-metered dry powder inhaler intended for use in the treatment of diseases of the respiratory tract (Module 2, Section 2.7.1). (b) (4)

. Acclidinium bromide Inhalation powder will be the first product to use the multi-dose device-metered dry powder inhaler (DPI) to be approved by the US FDA for its intended use. With the Almirall Inhaler, the formulation (b) (4)

(b) (4)

“(Slightly different versions of the Almirall inhaler (b) (4) were used in clinical studies during the development of acclidinium bromide (b) (4) 400 µg inhalation powder as shown in Section 3.2.P.2.4. However, it is important to note that the dose range finding studies and the Phase 3 clinical studies for the BID program were performed with the same (b) (4) device. The final inhaler version (b) (4) was used in the BID Phase 3 program and primary stability batches and represents the product intended for marketing.” [pg. 21, 2.3.P]

It may be noted that the *Almirall inhaler* used in clinical studies used formulations that contained (b) (4) α-lactose monohydrate. See pg. 18 of 3.2.P.2.2 for the compositions of formulations used during clinical development.

Dose proportionality:

“The delivered dose and fine particle fraction from the device have been found to be *proportional* to the dose. A strong linear correlation is observed between the product strength and the delivered dose throughout the (b) (4) product strength range. The fine particle dose is directly proportional to the delivered dose in this range as well.” [pg. 21, 2.3.P]

Excipient:

“No further processing aids or gases that could appear in the final formulation are used in drug product manufacture. α-Lactose monohydrate is the only *excipient* used in the formulation. Due to its particle size the lactose is too large to penetrate beyond the pharynx and upper airways resulting mainly in oral uptake of the excipient. The overall concentration of lactose in the formulation is approximately (b) (4) which is equivalent to a (b) (4) daily dose. This is well within the range of regular oral intake of lactose used in other products, for example products delivered via the Diskhaler® employ a (b) (4) carrier dose of lactose.” [pg. 22, 2.3.P]

Manufacturing process and manufacturing site:

It is indicated that the *manufacturing process* proposed for commercial product is the same as that used for Phase 3 and NDA stability batches. “The Phase 3 clinical batches and the NDA registration batches have been manufactured at the commercial manufacturing site at (b) (4), which is the proposed commercial batch size.” [pg. 23, 2.3.P] “The pivotal clinical and NDA registration batches (acclidinium bromide inhalation

powder) were manufactured at Forest Laboratories Ireland Limited, Clonsaugh Business & Technology Park facility in Dublin, Ireland (Forest Ireland). The commercial manufacturing of the drug product will be performed at the same site and utilize the same formulation, manufacturing process, equipment and scale as that used for the pivotal clinical and NDA registration batches.” [3.2.P.3.1] Earlier batches had been manufactured at (b) (4) and prior to that, at (b) (4)

Phase 3 change:

A change in Phase 3 trials from QD to BID dosing led to a change in drug product only involving the (b) (4), according to the applicant [2.3.P, pg. 23] See 3.2.P.2.3.2.5 for information about the change in device configurations. The applicant describes (b) (4) that were changed to 60 dose – 60 count devices (60D-60C) for additional phase 3 batches and primary NDA stability batches. The only difference between (b) (4) (b) (4). In vitro data were generated to compare these two devices. [pg. 25-28, 2.3.P] The 60D-60C device is that intended for marketing.

Characterization studies:

Characterization studies of the drug product are summarized on pages 29-40 of Section 2.3.P. Example highlights are mentioned below.

The delivered dose is indicated. Using the first three QD phase 3 clinical trial batches, it is claimed that a consistent dose was delivered across a flow rate range of (b) (4), and a consistent APSD and fine particle dose resulted over a flow rate range of (b) (4). The applicant states that “even the lowest patient inspiratory flow rates observed in clinical trials are sufficient to deliver an adequate fine particle dose.” (2.3.P, pg. 30).

Comment: reviewer should confirm the last statement above, pertaining to the lowest observed patient inspiratory flow rates vs. the flow range used in *in vitro* testing.

Device orientation during use should be horizontal according to the patient labeling (with the green button on top). A study indicated that device orientation 45 degrees upward or downward from the horizontal axis did not affect performance of the device.

Comment: applicant should indicate the effect on the performance if the device is horizontal but inverted.

Fine particle fraction is said to be dose proportional between (b) (4) 400 mcg presentations of the product. Stability testing did not show “remarkable” APSD

differences over 12 months on stability (based on single stage data, fine particle dose and grouped stages). Stability testing was performed using a single dose for APSD testing.

The drug product in in-use testing is said to be stable over the in-use life, after open storage at 25°C/75%RH and at 20°C/~35%RH. (Section 2.3.P pg. 33)

Multiple dose delivery (due to multiple pressing of the dosage key) is said to be not possible due to a prevention mechanism.

Other robustness tests are discussed.

Extractables and leachables:

Extractables and leachables were studied from the perspective of the PQRI recommendations. Extractable details are referenced to DMF (b) (4). None of the observed extractables were observed as leachables in the drug formulation powder after protected storage at 25°C/60%RH for up to 24 months (with the exception of some unknown unspecified peaks (maximum (b) (4))), therefore routine testing for leachables is viewed by the applicant as unnecessary. Routine extractables testing is performed to limit extractables in polymeric components (see Section 3.2.P.2.4, pp. 85-93). For leachables results, see pp. 94-95.

Comment: The reviewer should assess whether there is an extractable/leachable correlation (as described in the PQRI proposal for Orally Inhaled and Nasal Drug Products).

Drug products returned from the clinical studies:

Complaint devices in clinical trial LAS-MD-33 were evaluated. Out of 143 inhalers investigated, no defect was found in 137 inhalers. The other 6 devices were investigated further. See section 3.2.P.2.4 pp. 96-100. No “Class 1” or “Class 2” defects were observed (per the document: emea/ins/gmp/313510/2006, found on the internet, Class 1 and Class 2 defects are defects that may be potentially life threatening (1) or may cause illness or mistreatment (2)).

Complaint devices from the clinical trial M/34273/34 were assessed. Of 42 returns (out of 8280 inhalers used in the study), 35 were found to have no defect. The others were assessed. No “Class 1” or “Class 2” defects were observed (per the document: emea/ins/gmp/313510/2006, found on the internet, Class 1 and Class 2 defects are defects that may be potentially life threatening (1) or may cause illness or mistreatment (2)).

Fifty non-complaint devices from the clinical trial LAS-MD-34 were returned and examined. These yielded a low percentage of “pharmaceutical-technical complaints,” none of which was considered to be critical for the patient’s safety.

Products returned from the clinical study were also tested for DCU, APSD, related substances, (b) (4) microbial analysis, device functionality, lock out mechanism functionality, device resistance, and powder residue. The only notable observations were that some of the inhalers showed higher device resistance (and lower flow rates) compared to the release specification. This was attributed to accumulation of powder particles within the “sheath flow area” which the applicant feels may have been caused by patient misuse (e.g., exhaling into the inhaler). The applicant believes that even for these inhalers, their flow rates are still within the usability range for patients, where there is still constant fine particle dose delivery. (Section 2.3.P pg. 39).

Comment: reviewer should assess whether these failures seen in complaint devices and normally functioning devices represent significant safety concerns in terms of design problems, etc. A CDRH consult should be considered for such assessment as well.

Batch formula:

Table 3.2-1. (b) (4) Batch Formula for Acridinium bromide Inhalation Powder, 400 µg

<i>Component</i>	<i>Quality Standard</i>	<i>%w/w</i>	<i>Theoretical Weight (mg/dose)</i>	<i>Theoretical Weight (g/batch)</i>
Micronized Acridinium bromide	In-house standard ^a	(b) (4)	(b) (4)	(b) (4)
α-Lactose monohydrate (b) (4)	In-house standard ^b			
Total (b) (4)		100.0	13.0	(b) (4)

- a Per specification provided in Section 3.2.S.4.1 Specifications (Acridinium bromide micronized, (b) (4))
- b Per specification provided in Section 3.2.P.4.1 Specifications (Acridinium bromide Inhalation Powder, 400 µg).
- c The actual amount of acridinium bromide is calculated based (b) (4)

Table 3.2.P.3.2-2. Proposed Commercial Batch Size for Acridinium bromide Inhalation Powder, 400 µg

<i>Component</i>	<i>Batch Size</i>
Acridinium bromide Inhalation Powder (b) (4)	(b) (4)
Total (Theoretical) Number of DPI units	(b) (4)

- a The (b) (4) is filled into 60-count cartridges (b) (4)

The proposed commercial batch size is (b) (4) (formulation (b) (4) is filled into 60 count cartridges, (b) (4)), yielding (b) (4) DPI units (100% theoretical yield). A description of the process and process controls are provided (pg. 46-50, section 2.3.P). In-Process tests include (b) (4), fill weight, various description tests, and seal integrity.

Manufacturing:

Critical manufacturing steps are [REDACTED] (b) (4)

Excipient: Information about alpha-lactose monohydrate [REDACTED] (b) (4) excipient is referenced to DMF [REDACTED] (b) (4). The NDA contains specifications for this lactose (Section 3.2.P.4, pp. 1-3), including specifications from the USP/NF monograph on alpha-lactose monohydrate as well as other specifications).

Comment on lactose specifications: unless their absence is justified, we should request the following additional specifications for lactose: amorphous content, and particle shape and morphology.

Drug Product Specifications:

Specifications are provided in Section 3.2.P.5.1. See below.

Table 3.2.P.5.1-1. Specification for Acclidinium bromide Inhalation Powder, 400 µg

<i>Test</i>	<i>Acceptance Criteria</i>	<i>Method</i>
Description (Almirall Inhaler)^a	White inhaler with a green protective cap, green dosage key and a fixed slide cover with a cartridge including a 60 dosages counter ring inside, containing the medication	Visual
Description (Contents of Cartridge)^a	White or almost white powder (b) (4) free flowing, without visible agglomerates or foreign particulates	Visual
Identification Acclidinium bromide (HPLC)^a	The deviation of the retention time of Acclidinium bromide in test solution and reference solution not more than (b) (4)	HPLC
Identification Acclidinium bromide (HPLC/UV diode array)	UV-spectrum conforms to reference spectrum	HPLC/UV diode array detection
Identification α-Lactose monohydrate (IR)	IR-spectrum conforms to reference spectrum	IR
Filling per cartridge^a	(b) (4)	Gravimetrically
Number of Doses per Cartridge^a	Not less than (NLT) 60	Visual
Degradation Products^a	(b) (4) NMT	UPLC
	(b) (4) NMT	
	(b) (4) NMT	
	Total (b) (4) NMT	
(b) (4)		
Color^a	Not more intense than (b) (4)	Visual

Table 3.2.P.5.1-1. Specification for Acclidinium bromide Inhalation Powder, 400 µg

<i>Test</i>	<i>Acceptance Criteria</i>	<i>Method</i>
Content of Acclidinium bromide per Cartridge^a	Individual Values (b) (4)	HPLC/UV detection
	Mean Value	
	Individual Values (% NC)	
	Mean Value (% NC)	
	Mean Value (mg/Sample)	

Table 3.2.P.5.1-1. Specification for Acridinium bromide Inhalation Powder, 400 µg

<i>Test</i>	<i>Acceptance Criteria</i>		<i>Method</i>
Dose Content Uniformity^a	Individual Values (% LC)	Table 3.2.P.5.1-2	HPLC/UV detection
	Mean Value Beginning (% LC)	(b) (4)	
	Mean Value Middle (% LC)	(b) (4)	
	Mean Value End (% LC)	(b) (4)	
Particle Characterization Aerodynamic Assessment of Fine Particles^a	(b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4) HPLC
	(b) (4)	NMT (b) (4)	(b) (4)
	Total Sum (5 Samples)	(b) (4)	(b) (4)
Foreign Particulate Matter (Maximum amount of foreign particles)	(b) (4)	(b) (4) particles/dose	based on USP Chapter <788>
	(b) (4)	particles/dose	
	(b) (4)	particles/dose	
Microbiology^a	Total aerobic microbial count (TAMC)	NMT (b) (4)	Current USP/NF Chapter <61> and Chapter <62> (membrane filtration method)
	Total combined yeasts/molds count (TYMC)	NMT (b) (4)	
	Bile tolerant Gram - negative bacteria	Absence in (b) (4)	
	<i>Pseudomonas aeruginosa</i>	Absence in (b) (4)	
	<i>Staphylococcus aureus</i>	Absence in (b) (4)	

^a Bolded Tests are for release and stability evaluation.

NC = Nominal Claim (b) (4) LC = Label Claim (375 µg/dose): delivered dose.

Table 3.2.P.5.1-2. Dose Content Uniformity Acceptance Criteria for Acclidinium bromide Inhalation Powder, 400 µg Based on FDA Guidance Document Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Dated November 13, 1998

<i>Level and Number of Units Tested</i>	<i>Release Criteria</i>	<i>Stability Criteria</i>
L ₁ (ten inhalers / 3 actuations per inhaler)	The amount of active ingredient per determination is not outside of 80-120 percent of label claim for more than three of thirty determinations from ten inhalers; none of the determinations is outside of 75-125 percent of the label claim.	The amount of active ingredient per determination is not outside of 75-125 percent of label claim for more than one of thirty determinations from ten inhalers; none of the determinations is outside of 65-135 percent of the label claim.
L ₂ <i>Extended acceptance criteria (twenty additional inhalers):</i> If four to nine of the thirty determinations are outside of 80-120 percent of the label claim, none is outside of 75-125 percent of label claim, and the means for each of the beginning, middle, and end determinations are not outside of 85-115 percent of label claim, an additional twenty inhalers should be sampled (second tier)	For the second tier of testing of a batch, the amount of active ingredient per determination is not outside of 80-120 percent of the label claim for more than 9 of all 90 determinations, none of the 90 determinations is outside of 75-125 percent of label claim, and the means for each of the beginning, middle, and end determinations are not outside of 85-115 percent of label claim.	N/A
L ₂ <i>Extended acceptance criteria (twenty additional inhalers):</i> If two to three of the thirty determinations are outside of 75-125 percent of the label claim, none is outside of 65-135 percent of label claim, and the means for each of the beginning, middle, and end determinations are not outside of 85-115 percent of label claim, an additional twenty inhalers should be sampled (second tier).	N/A	For the second tier of testing of a batch, the amount of active ingredient per determination is not outside of 75-125 percent of the label claim for more than 3 of all 90 determinations, none of the 90 determinations is outside of 65-135 percent of label claim, and the means for each of the beginning, middle, and end determinations are not outside of 85-115 percent of label claim.

Comment: The drug product attributes (qualitatively) include those recommended in the MDI/DPI draft guidance.

Analytical procedures are listed in Section 3.2.P.5.2 with method titles, method numbers and method type.

Impurities:

In NDA section 3.2.P.5.5, 8 specific impurities are listed which have been observed in some batches. Three are listed as having DEREK structural alerts for genotoxicity. Of these three structure alerts, two are said to be negative in bacterial reverse mutation assays, and one (b) (4) is positive. The applicant states that they control the (b) (4) in the drug substance to less than the TTC of (b) (4) mcg/day.

Comment: Impurity levels should be assessed for safety by pharm/tox reviewers, especially for impurities with structure alerts.

Validation of analytical procedures – Section 3.2.P.5.3.

Summary of information pertaining to the registration batches, see pg. 56 of 2.3.P. and see below. Note that two batches used (b) (4) the formulation, from the beginning, middle and end of the filling run and the units filled were assembled into the final inhaler device. As noted earlier, (b) (4) is the batch size of the intended commercial production.

Table 5.4-1. Batch Information for the NDA Registration Batches of Acclidinium bromide Inhalation Powder, 400 µg

Drug Product			Drug Substance Lot #	α-Lactose monohydrate Excipient Lot #	Date of Manufacture	Batch Size	Packaging	Use
Batch #	Stage of Operation	Stage of Operation Lot #						
DPI047	(b) (4)			(b) (4)	(b) (4)	(b) (4)	Aluminum foil pouch containing Almirall inhaler	NDA Registration / Phase 3 Clinical Trials
DPI048							Aluminum foil pouch containing Almirall inhaler	NDA Registration / Phase 3 Clinical Trials
DPI049							Aluminum foil pouch containing Almirall inhaler	NDA Registration

a Approximately (b) (4) filled cartridges from the beginning, middle and end of the production filling process were assembled into the final inhaler device.

NDA Stability Studies: “The Acclidinium bromide Inhalation Powder, 400 µg strength NDA registration batches samples were stored on stability according to the ICH Q1A (R2) Stability Testing of New Drug Substance and Products using storage design that covers ICH and the FDA requirements (Type C-CMC meeting, May 12, 2009: inverted and upright orientations at the following conditions: 40°C/75%RH, 30°C/65%RH, 25°C/60%RH, and 25°C/75%RH). Real time data up to 12 months are submitted in the NDA.” [quote from pg. 60, 2.3.P] Note that 6 months data are provided for the 40°C/75% storage conditions. See earlier information in this IQA which states that the stability batches are the same as those intended for marketing.”

“The [primary stability] batches are evaluated under ICH conditions as stated earlier in this section and are monitored for the following parameters; descriptions, identification acclidinium bromide, filling per cartridge, number of doses per cartridge, (b) (4) color, content of acclidinium bromide per cartridge, dose content uniformity, aerodynamic particle size distribution and microbial limits.” [pg. 61, 2.3.P] It is stated that mean stability results were within specification limits [what about individual results?], that no significant trends were observed on stability, and that the different storage orientations did not have any effect on product stability. “The detailed results of all the stability

indicating attributes including mean and individual data are presented in Section 3.2.P.8.3 *Stability Data.*”

“No increase of foreign particles could be observed during the stability studies. Since the amount of foreign particles remained constant, it is unlikely that the kind of particles has changed. Therefore, testing of foreign particles will only be conducted on release of the drug product by light obscuration and no testing will be performed on stability.” [quoted from 2.3.P, page 57).

Comment: Graphical plots are provided for stability data for some parameters (e.g., dose content uniformity, aerodynamic particle size distribution). SAS transport files are said to be provided but they are not evaluated here.

Other stability studies which were conducted include in-use stability and photostability studies. No stability concerns are indicated by the applicant for the in use studies (through 12 months) and for the photostability studies (the drug product is said not to be photosensitive).

Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED
(b) (4)	IV	(b) (4)	(b) (4) (DMF was first received on 4/11/2011 and has never been reviewed.)
	III		(b) (4) DMF was first received on 1/19/11 and has never been reviewed.)
	II		micronized acclidinium bromide (DMF was reviewed, once, by Dr. Prasad Peri on 3/15/2004 and found adequate for an IND.) This DMF was completely updated (7 volumes) on 4/29/11 (date of submission).

Supporting Device Master File (MAF): [if relevant]

N.A.

Letters of authorization for the above DMFs: yes, these are provided (Section 1.4.1).

IND for this drug product: IND 68653

related IND 72252 (for acclidinium bromide and formoterol fumarate for COPD)

Filing Check List:

	Parameter	Yes	No	Comment
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1	On its face, is the section organized adequately?	x		
2	Is the section indexed and paginated adequately?	x		
3	On its face, is the section legible?	x		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	x		
5	Is a statement provided that all facilities are ready for GMP inspection?	x		Exception: This is indicated for drug product facilities (in P.3.1), but not for drug substance facilities (in S.2.1)
6	Has an environmental assessment report or categorical exclusion been provided?	x		(b) (4)
7	Does the section contain controls for the drug substance?	x		<p>The NDA contains specifications for micronized drug substance only, but not the (b) (4)</p> <p>Check the drug substance DMF for (b) (4) specifications.</p> <p>Note that the (b) (4) (b) (4) specifications ((b) (4) micronized drug substance) should be in the NDA.</p>
8	Does the section contain controls for the drug product?	x		
9	Have stability data and analysis been provided to support the requested expiration date?	x analy sis is thin		<p>Drug product stability data are provided for three batches, manufactured at commercial scale and site. The 400 mcg formulation, manufacturing process and device are said to be unchanged from phase 3 clinical studies through NDA stability batches and proposed commercial drug product. Real time data are provided through 12 months (using ICH storage conditions). A shelf life of 24 months is proposed for the 400 mcg drug product.</p>

			<p>The missing stability attribute is foreign particulate matter. Dose content uniformity acceptance criteria on stability through product life appear to only require (b) (4) of nominal dose. This will be improved in the proposed commercial specification. Full stability time points were evaluated for inverted product, but upright product was only stability tested at annual intervals (25°C). It appears that the only regression analysis reported was on 12 months of data (for the parameter, “mean content per cartridge” data only). Note that a cartridge contains 60 doses. Acceptability of the expiry date is a review decision. Additional regression analyses for other stability parameters may be necessary in order to consider the proposed shelf life, especially since 12 months of data are provided for a proposed 24 month expiry, but this is a review decision.</p> <p>Note that drug substance stability data are referenced to DMF (b) (4), and data up to 48 months are indicated to be available for two batches, and 24 months for a third batch.</p>
10	<p>Has all information requested during the IND phase, and at the pre-NDA meetings been included?</p>		<p>In the IND meetings, there was considerable discussion and significant details of CMC data that should be provided, in submission of the NDA. Whether all of the requested information has been provided in the NDA is a review issue.</p>

11	Have draft container labels been provided?	x		
12	Has the draft package insert been provided?	x		
13	Has an investigational formulations section been provided?	x		
14	Is there a Methods Validation package?		x	package per the guidance was not found (e.g. in 3.2.R)

Certain review issues which were noted are listed below for consideration by the reviewer

The applicant states that “even the lowest patient inspiratory flow rates observed in clinical trials are sufficient to deliver an adequate fine particle dose.” (2.3.P, pg. 30). The reviewer should confirm the last statement above, pertaining to the lowest observed patient inspiratory flow rates vs. the flow range used in *in vitro* testing.

The reviewer should assess whether the failures seen in complaint devices and normally functioning devices (obtained from drug product used in clinical trials) represent significant safety concerns in terms of design problems, etc.

Assess the data provided to justify lack of testing of foreign particles on stability. It is proposed to only test this attribute at release. [2.3.P, pg. 57]

Once a methods validation package has been received, a methods validation request should be submitted to the CDER St. Louis laboratory, since this product is an NME. Suggested methods to be validated/verified include dose content uniformity and aerodynamic particle size distribution.

A consult is recommended for drug product microbial limits testing; however, USP <61>, <62> and <1111> are referenced, with no actual method description provided. It should be determined first whether the USP description for microbial limits testing is adequate, or if the method used should be fully described. The justification for lack of microbial limits testing of the drug substance should be evaluated.

The reviewer should see whether adequate data are provided to justify not testing the amorphous content of the drug substance on stability.

The reviewer should assess whether there is an extractable/leachable correlation (as described in the PQRI proposal for Orally Inhaled and Nasal Drug Products).

We should request the following additional specifications for lactose: amorphous content, and particle shape and morphology, unless absence of these specifications is adequately justified.

Reviewer should check for additional (other than reported) characterization tests that are typically recommended for DPIs, e.g. device robustness and ruggedness, dose buildup and cleaning instructions, profiling of doses near reservoir exhaustion, molding tool scale up, and microscopic evaluation.

Comments for applicant:

Clarify what acceptance and release testing you will routinely perform on receipt of the drug substance and the lactose excipient.

Provide full drug substance specifications to the NDA (i.e. a list of tests, acceptance criteria and analytical procedures), and validation data for the analytical methods for the drug substance, since you need to be able to periodically verify the information on the certificates of analysis for the drug substance.

Provide full excipient (lactose monohydrate) specifications to the NDA (i.e. a list of tests, acceptance criteria and analytical procedures), and validation data for the analytical methods for the excipient, since you need to be able to periodically verify the information on the certificates of analysis.

Provide drug product characterization data to demonstrate the effect on the performance of the drug product if the device is horizontal but inverted.

Provide a statement that all drug substance facilities are ready for GMP inspection.

As part of your request for a categorical exclusion, provide a statement pertaining to extraordinary circumstances pursuant to 21 CFR 25.15. Extraordinary circumstances are defined in 21 CFR 25.21.

Include in the NDA specifications for the [REDACTED] (b) (4) as well as the micronized drug substance.

Provide a methods validation package as indicated in our guidance, *Guideline for Submitting Samples and Analytical Data for Methods Validation*.

IND Information particularly relevant to CMC review:

Device changes were discussed at the EOP2 meeting.

A change in the drug product manufacturing site was discussed at the EOP2 meeting.

Potential genotoxic impurities and stability data were discussed at the preNDA CMC meeting.

All minutes of IND meetings pertaining to CMC issues are worth reviewing prior to review of the NDA.

Recommendation:

**Fileable from CMC perspective
EES – status is “pending”**

Recommend a pharm/tox consult for impurities/degradants/leachables, and possibly a CDRH consult for evaluation of complaint inhaler investigations

Methods validation to be requested since this drug is an NME.

Attachment A: Nanotechnology product evaluating questions:

<p>1, This review contains new information added to the table below: <input checked="" type="checkbox"/> Yes; <input type="checkbox"/> No</p> <p>Review date: _____</p>
<p>2) Are any nanoscale materials included in this application? (If yes, please proceed to the next questions.) Yes _____; No <input checked="" type="checkbox"/>; Maybe (please specify) _____</p>
<p>3 a) What nanomaterial is included in the product? (Examples of this are listed as search terms in Attachment B.) _____</p>
<p>3 b) What is the source of the nanomaterial? _____</p>
<p>4) Is the nanomaterial a reformulation of a previously approved product?</p> <p>Yes _____ No _____</p>
<p>5) What is the nanomaterial functionality?</p> <p>Carrier _____; Excipient _____; Packaging _____</p> <p>API _____; Other _____</p>
<p>6) Is the nanomaterial soluble (e.g., nanocrystal) or insoluble (e.g., gold nanoparticle) in an aqueous environment?</p> <p>Soluble _____; Insoluble _____</p>
<p>7) Was particle size or size range of the nanomaterial included in the application?</p> <p>Yes _____ (Complete 8); No _____ (go to 9).</p>
<p>8) What is the reported particle size?</p> <p>Mean particle size _____; Size range distribution _____; Other _____</p>
<p>9) Please indicate the reason(s) why the particle size or size range was not provided:</p> <p>_____</p> <p>_____</p>
<p>10, What other properties of the nanoparticle were reported in the application (See Attachment E)? _____</p>
<p>11) List all methods used to characterize the nanomaterial? _____</p> <p>_____</p>

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
08/26/2011

PRASAD PERI
08/26/2011
I concur