CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202450Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 202450 SUPPL # HFD #

Trade Name Tudorza Pressair

Generic Name Aclidinium Bromide

Applicant Name Forest Laboratories, Inc.

Approval Date, If Known July 23, 2012

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(1)

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

YES ☒ NO ☐

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

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

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

5 years

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☒

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

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

1. Single active ingredient product.

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

YES ☐ NO ☒

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

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

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

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

YES ☐ NO ☐

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

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

YES ☐ NO ☐

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

YES ☐ NO ☐

If yes, explain:

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

YES ☐ NO ☐

If yes, explain:

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

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

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

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

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

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

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

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

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

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

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

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Sadaf Nabavian
Title: Regulatory Project Manager
Date: July 23, 2012

Name of Office/Division Director signing form: DPARP/Badrul A. Chowdhury, M.D., Ph.D.
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

SADAF NABAVIAN
07/23/2012

BADRUL A CHOWDHURY
07/23/2012

DEBARMENT CERTIFICATION

Forest Laboratories, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Joseph S. Camardo, MD
Senior Vice President, Clinical Development -
Respiratory and Medical Affairs
Forest Research Institute, Inc.
A subsidiary of Forest Laboratories Inc.

April 29, 2011
Date

NDA 202450
Aclidinium Bromide
Forest Laboratories

Dear Dr. Iqbal:

Your NDA submission dated, June 23, 2011, for aclidinium bromide is currently under review. We are providing additional labeling comments. Submit revised labeling incorporating the changes shown in the attached marked up label via email to Sadaf.Nabavian@fda.hhs.gov by the close of business on July 19, 2012. Please note that we may have additional labeling comments as we continue the review of your application. The email should be followed by an official submission to the NDA.

If there are any questions, contact Sadaf Nabavian, Regulatory Management Officer at 301-796-2777.

Drafted by: SNabavian/07.18.2012

Cleared by: LJafari/07.18.2012

Finalized by: SNabavian/07.18.2012

23 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

SADAF NABAVIAN
07/18/2012

NDA 202450
Aclidinium Bromide
Forest Laboratories

Dear Dr. Iqbal:

Your NDA submission dated, June 23, 2011, for aclidinium bromide is currently under review. We are providing additional preliminary labeling comments. Submit revised labeling incorporating the changes shown in the attached marked up label via email to Sadaf.Nabavian@fda.hhs.gov by the close of business on July 18, 2012. Please note that we may have additional labeling comments as we continue the review of your application.The email should be followed by an official submission to the NDA.

If there are any questions, contact Sadaf Nabavian, Regulatory Management Officer at 301-796-2777.

Drafted by: SNabavian/07.16.2012

Cleared by: LJafari/07.16.2012

Finalized by: SNabavian/07.16.2012

23 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

SADAF NABAVIAN
07/16/2012

NDA 202450
Aclidinium Bromide
Forest Laboratories

Dear Dr. Iqbal:

Your NDA submission dated, June 23, 2011, for aclidinium bromide is currently under review. In addition to our comment listed below, we also proposed insertions (underlined) and deletions (strike-out) in the attached documents. These comments are not all-inclusive and we may have additional comments and/or requests as we continue our review of the label.

Submit revised labeling incorporating the changes shown in the attached marked up label and our comment noted below, via email to Sadaf.Nabavian@fda.hhs.gov by the close of business on Friday, July 13, 2012. The email should be followed by an official submission to the NDA. If there are any questions, contact Sadaf Nabavian, Regulatory Management Officer at 301-796-2777.

A. The following comment pertain to the Instructions for Use (IFU) Labeling

1. To improve legibility and readability, change the color of the borders for the boxed figures, check marks, and "X" marks to black in Figures B-P.

Drafted by: SNabavian/7.10.12
Cleared by: LJafari/7.10.12
Finalized by: SNabavian/7.10.12

23 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

SADAF NABAVIAN
07/10/2012

NDA 202450
Aclidinium Bromide
Forest Laboratories

Dear Dr. Iqbal:

Your NDA submission dated, June 23, 2011, for aclidinium bromide is currently under review. In addition to the comments listed below, we also proposed insertions (underlined) and deletions (strike-out) in the attached documents. These comments are not all-inclusive and we may have additional comments and/or requests as we continue our review of the label.

Submit revised labeling incorporating the changes shown in the attached marked up label and our comments noted below, via email to Sadaf.Nabavian@fda.hhs.gov by the close of business on July 3, 2012. The email should be followed by an official submission to the NDA. If there are any questions, contact Sadaf Nabavian, Regulatory Management Officer at 301-796-2777.

A. The following comments pertain to the Patient Information and Instructions for Use (IFU) Labeling

We acknowledge your submission dated June 11, 2012, which was in response to our communications dated March 30, and June 4, 2012. The Patient Labeling has been extensively revised and reformatted. Please make all revisions using this version in order to preserve these formatting changes. Please note our revisions were done using the original NDA submission dated June 23, 2011. The current document we are providing takes into account both our current recommendations, as well as the changes included in our March 30, and June 4, 2012, communications.

1. Do not use all capital letters in patient labeling as it difficult for patients with low vision to read.
2. Insert the phonetic spelling of the trade name where indicated.
3. Insert the website where indicated, if applicable.
4. Label the first figure "Figure A" where indicated.
5. Change the label of the current (b) (4) to "Figure B."
6. Change the label of the current (b) (4) to "Figure C." Revise this image to include a figure of a face with the device facing the patient's mouth.
7. Change the label of the current (b) (4) and (b) (4) to "Figure D" and "Figure E." Both here and throughout the document, use black font for all instructions to patient. In addition, use bolded text instead of underlying to highlight important information.
8. The layout of the current (b) (4) have been switched, so that (b) (4) (red control window) is to the left of (b) (4) (green control

window). Change the label of [redacted] to "Figure F" and [redacted] to "Figure G."

9. Change the label of the current [redacted] to "Figure H" and "Figure I" where indicated.
10. Add a Figure J where indicated illustrating the new Step 6.
11. Change the label of the current [redacted] and [redacted] to "Figure K" and "Figure L."
12. Change the label of the current [redacted] to "Figure M."
13. Insert the current [redacted] and label as "Figure N" where indicated.
14. Insert the current [redacted] and [redacted] where indicated and label as "Figure O" and "Figure P."

B. The following pertains to all Device Labels, Carton Labeling, Early Experience Program Professional Sample Labeling, and Pouch Labeling

1. Remove the graphic located next to the proprietary name so it does not distract from the prominence of the proprietary name.

27 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

SADAF NABAVIAN
06/28/2012

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

Date: June 4, 2012, 2012

To: Dr. Amjad Iqbal Associate Director	**From:** **Angela Ramsey** **Project Coordinator**
Company: Forest Labs	**Division of Pulmonary, Allergy, and Rheumatology Drug Products**
Fax number: 631-858-7921	**Fax number:** **301-796-9728**
Phone number: 201-386-2117	**Phone number:** **301-796-2284**

Subject: NDA 202450 Aclidinium Bromide labeling fax# 2

Total no. of pages including cover:

Comments:

Document to be mailed: YES XNO

NDA 202450

Your NDA submission dated, June 23, 2011, for aclidinium bromide is currently under review, and we have a request for labeling revisions. The FDA-proposed insertions are underlined and deletions are in strike-out. These comments are not all-inclusive and we may have additional comments and/or requests as we continue our review of the label.

Submit revised labeling incorporating the changes shown in the attached marked up label for the Package Insert via email to angela.ramsey@fda.hhs.gov by June 11, 2012. The email should be followed by an official submission to the NDA.

If there are any questions, contact Angela Ramsey, Senior Regulatory Management Officer at 301-796-2284.

20 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

ANGELA H RAMSEY
06/04/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202-450

INFORMATION REQUEST

Forest Laboratories, Inc.
Attention: Blake Burrell, M.S. RAC
Senior Manager, Regulatory Affairs-CMC
Harborside Financial Center
Plaza V, Suite 1900
Jersey City, NJ 07311

Dear Mr. Burrell:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aclidinium Bromide, Inhalation Powder.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response (preferably by May 11, 2012) in order to continue our evaluation of your NDA..

1. Method PRD-TM-ANL-00484 for Dose Content Uniformity.
   - On page 7, the method states (b) (4)
   - On page 7, the method states that (b) (4)

2. Methods PRD-TM-ANL-00482 and PRD-TM-ANL-00412 for Aerodynamic Particle Size Distribution
   - Clarify how the cutoff diameters of each of the stages of the impactor are determined at the individual flow rates used in the individual test runs.
   - Correct (b) (4)) to "Mass Median Aerodynamic Diameter".

3. Provide a written commitment and timeline (e.g. timeframe for completion and regulatory submission) to re-evaluate the aerodynamic particle size distribution specification for the drug product after you have accumulated sufficient batch data (e.g., 15 batches).

If you have any questions, contact Youbang Liu, Regulatory Project Manager, at (301) 796-1926.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

PRASAD PERI
05/04/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 21, 2012

TO: Forest Laboratories

THROUGH: Imjad Iqbal

FROM: OND/DPARP

SUBJECT: Post Wrap-Up teleconference

APPLICATION/DRUG: NDA 202450/Aclidinum bromide

The purpose of the wrap-up teleconference with Forest Laboratories was to provide a review status update on NDA 202450 and to discuss plans for proposed PMR as recommended during February 23, 2012 Advisory Committee meeting.

Status Update:
Reviews are pending. Division received revised SGRQ data which will require additional time to review; therefore PDUFA clock was extended with a new PDUFA goal date of July 23, 2012. There are pending issues as discussed in CMC teleconference on March 20, 2012 regarding acceptance criteria; therefore, CMC review is on-going.

Proposed PMR
The Division discussed ethical concerns with COPD long- term trials and wash-out of baseline medications. Currently, the Division does not have answers to address this issue, but is open to any suggestions related to wash-out issue. Forest proposed (b) (4) . Forest will provide a more refined program that will address Advisory Committee feedback and the Division's concerns.

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

/s/

ANGELA H RAMSEY
04/17/2012

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

Date: March 30, 2012

To: Dr. Amjad Iqbal Associate Director	**From:** **Angela Ramsey** **Project Coordinator**
Company: Forest Labs	**Division of Pulmonary, Allergy, and Rheumatology Drug Products**
Fax number: 631-858-7921	**Fax number:** **301-796-9728**
Phone number: 201-386-2117	**Phone number:** **301-796-2284**

Subject: NDA 202450 Aclidinium Bromide labeling fax# 1

Total no. of pages including cover:

Comments:

Document to be mailed: YES XNO

NDA 202450

Your NDA submission dated, June 23, 2011, for aclidinium bromide is currently under review. Comments relating to specific sections can be found below. These comments are not all-inclusive and we may have additional comments and/or requests as we continue our review of the label.

A. Package Insert Labeling

1) General

   a) Update the tradename throughout the document.

   b) Remove all trailing zeros except for where necessary to demonstrate the level of precision of the value being reported.

   c) Revise the labeling to replace the symbols <, ≤, >, ≥, with text.

   d) When presenting numbers with symbols or units, insert a space between the number and the symbol, or unit, to provide better readability (e.g., "2 L" instead of "2L").

   e) Add a unit of measure immediately following all numbers, as appropriate (e.g. "doses of 4.8 mg/kg/day and 3.6 mg/kg/day" instead of "doses of up to 4.8 and 3.6 mg/kg/day").

   f) Keep numbers next to units or symbols within the same line of text.

   g) Revise numbers greater or equal to 1,000 so that a comma is included (e.g. 6,000 instead of 6000).

2) Section 6.1

   a) Provide a reference for the baseline mean FEV1 of 48% (e.g., table number, submission date) so we may confirm this number.

   b) Provide a summary of the long-term safety data where indicated.

3) Section 10.1

   a) The reference provided in the annotated label states that there were (b) (4) healthy human subjects, not 6. Clarify the discrepancy.

4) Section 12:2

a) The "N" values provided here for the Holter monitoring subgroup differ from those reported in the table referenced by the annotated label. Clarify the discrepancy.

5) Section 14.1

a) Insert demographic data for the ITT population where indicated in the first paragraph.

B. All Device Labels, Carton Labeling, Early Experience Program Professional Sample Labeling, and Pouch Labeling

1. Minimize the graphic located to the right of the proprietary name so it does not distract from the prominence of the proprietary name.

C. Professional Samples and Trade Device Labels

1. Increase the prominence of the established name to be in accordance with 21 CFR 201.10(g)(2). Ensure the established name has prominence commensurate with the proprietary name taking into account all pertinent factors including typography, layout, contrast and other printing features.

2. Revise the strength statement to state 400 mcg per actuation and increase the font sizes for increased prominence.

3. Relocate the route of administration statement "For Oral Inhalation" to appear below the statement of strength.

4. Debold the "Rx Only" statement so it is less prominent.

D. Professional Sample Device Label.

1. Debold the font for "Professional Sample Not for Sale" so it is less prominent.

E. Demonstration Inhaler Device Label

1. Replace the name device name with the statement "Demonstration Inhaler for (b) (4)" We recommend using a larger font size for the words "Demonstration Inhaler" and a smaller font size for the words "for (b) (4)

2. Bold and change the font for the statements "INHALER FOR DEMONSTRATION…," "NOT FOR TEHRAPEUTIC…," and "CONTAINS NO MEDICINE…" from all uppercase (INHALER FOR DEMONSTRATION…) to title case (Inhaler for Demonstration…) to improve readability.

3. Clearly identify the demonstration inhaler as a demonstration device or trainer by increasing the prominence of the statement "Inhaler for Demonstration Purposes Only." To increase the prominence, we recommend placing a box around the statement and increasing the sizes of the statement within this box.

4. In order to increase differentiation between the demonstration inhaler and a medicine containing device, remove the graphic located to the right of the proprietary name.

F. Professional Samples Carton Labeling, Trade Carton Labeling and EEP (Early Experience Program) Professional Sample Labeling (tray, sleeve, and carton)

1. See comments C1 to C4 above.

2. Revise and bold the statement [redacted] (b) (4) to read **"Discard Tradename inhaler 45 days after opening the pouch…"** for clarity and increased prominence.

3. Debold the statement "See Package Insert…Instructions for Use."

G. Professional Samples Carton Labeling, EEP Professional Sample Sleeve, and EEP Sample Carton Labeling

4. See comment D above.

H. Aluminum Pouch Labeling (Professional Samples and Trade)

1. See comments C1 to C4 and F2 to F3 above.

2. Relocate the discard statement above the storage statement so that it immediately follows the statement to keep the inhaler inside the sealed pouch until the administration period starts. This will allow related information to read sequentially.

I. EEP Professional Sample Sleeve and Sample Carton Labeling

1. See comments C1 to C4, F2 to F3, and H2 above.

2. Identify where the expiration date and lot number will be printed on the sleeve and sample package labeling.

J. Demonstration Inhaler Carton and Aluminum Pouch Labeling

1. See comments E1 to E4 above.

Submit revised labeling incorporating the changes shown in the attached marked up label for the Package Insert via email to angela.ramsey@fda.hhs.gov by April 6, 2012. The email should be followed by an official submission to the NDA.

Drafted by: AR/March 12, 2012
Initialed by: SB/March 12, 2012; JP/March 29, 2012; SL/March 29, 2012; GL/March 13, 2012; TR/March 13, 2012; PP/March 19, 2012; YH/March 19, 2012; SD/March 14, 2012; FZ/March13, 2012; JB/March 13, 2012

Finalized: AR/March 30, 2012

20 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

ANGELA H RAMSEY
03/30/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202450

REVIEW EXTENSION – MAJOR AMENDMENT

Forest Laboratories, Inc.
Harborside Financial Center
Plaza V, Suite 1900
Jersey City, New Jersey 07311

ATTENTION: Amjad M. Iqbal, PharmD
Associate Director, Regulatory Affairs

Dear Dr.Iqbal:

Please refer to your June 23, 2011, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for aclidinium bromide inhalation powder.

On March 15, 2012, we received your March 14, 2012, unsolicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is July 23, 2012.

In addition, in accordance with the "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012," the timeline for communicating labeling changes and/or postmarketing requirements/commitments, provided in our September 2, 2011, filing communication letter, no longer applies and no new timeline will be provided.

If you have any questions, call Angela Ramsey, Senior Regulatory Project Manager at (301) 796-2284.

Sincerely,

{See appended electronic signature page}

Ladan Jafari
Chief, Project Management Staff
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

ANGELA H RAMSEY
03/19/2012
AR for LJ

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202450 **INFORMATION REQUEST**

Forest Laboratories, Inc.
Attention: Blake Burrell, M.S. RAC
Senior Manager, Regulatory Affairs-CMC
Harborside Financial Center
Plaza V, Suite 1900
Jersey City, NJ 07311

Dear Mr. Burrell:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aclidinium Bromide, Inhalation Powder.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response (preferably by March 12, 2012) in order to continue our evaluation of your NDA.

1. Revise your drug product aerodynamic particle size distribution (APSD) specification to tighten the ranges of acceptance criteria for Stage Groups 1 – 3 and Fine Particle Dose for individual determinations as follows.
   - Individual Group 1: (b) (4) µg;
   - Individual Group 2: (b) (4) µg;
   - Individual Group 3: (b) (4) µg;
   - Individual Fine Particle Dose: (b) (4) µg.

   The above ranges are based on our analysis for the APSD data for the full scale clinical and stability batches DPI028 (release), DPI047, DPI048, and DPI049 (release and stability) provided in the NDA. Note that accelerated stability data were not and should not be used in deriving acceptance criteria for the APSD specification.

2. We recommend that, instead of setting acceptance criteria for Total Sum (individual and mean) in the drug product specification, you include a relevant run qualification test for Individual Mass Balance of the total labeled (emitted) dose in your analytical methods for aerodynamic particle size assessment. If the run qualification criterion is not met during the analytical run, an investigation of the failure should be performed under your quality system. Revise the drug product specification and the APSD analytical methods accordingly.

3. Patient use of the drug product should be limited to your labeled number of doses (sixty doses). Therefore, the inhaler should be discarded when "0" (zero) appears in the dose

indicator. However, since the markings “10” and “0” show simultaneously in the dose indicator after 60 doses, it may be confusing to the patients how many doses are left. We suggest that you omit the “10” marking on the counter ring and fill the space by expanding the current red markings, or you may propose an alternative adequate solution.

4. Provide an explanation for, and resolve the following discrepancy. The calculation of minimum and maximum limits of cartridge weight for in-process testing (Step 2 under “Assembly” Section, Page 3 of 53) in the Master Batch Record resubmitted for the drug product does not appear to support the cartridge fill weight limits set in the drug product specification and is not consistent with the calculation used in the executed batch records.

If you have any questions, call Swati Patwardhan, Regulatory Project Manager-Quality, at 301-796-4085.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

PRASAD PERI
03/02/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202450

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Forest Laboratories, Inc.
Harborside Financial Center
Plaza V, Suite 1900
Jersey City, New Jersey 07311

ATTENTION: Amjad M. Iqbal, PharmD
Associate Director, Regulatory Affairs

Dear Dr. Iqbal:

Please refer to your New Drug Application (NDA) dated June 23, 2011, received June 23, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aclidinium Bromide Powder for Oral Inhalation, 400 mcg per actuation.

We also refer to your December 1, 2011, correspondence, received December 1, 2011, requesting review of your proposed proprietary name, Tudorza Pressair. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, Tudorza Pressair, will be re-reviewed 90 days prior to the approval of the marketing application. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your December 1, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Sadaf Nabavian, at (301) 796-2777.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

CAROL A HOLQUIST
02/21/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202450 **INFORMATION REQUEST**

Forest Laboratories, Inc.
Attention: Amjad M. Iqbal, Pharm.D.
Associate Director, Regulatory Affairs
Harborside Financial Center
Plaza V, Suite 1900
Jersey City, NJ 07311

Dear Dr. Iqbal:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aclidinium Bromide, Inhalation Powder.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. You have proposed different acceptance criteria for individual values of dose content uniformity testing for batch release and stability in Table 3.2.P.5.1-2. Batch release criteria may be applied as in- house specifications, however, there should be only one set of regulatory specifications which would be in effect from release through the end of the shelf life of the product. Based on your data, the proposed acceptance criteria currently set for release only in Table 3.2.P.5.1-2 should apply to both product release and stability.

2. Your analytical methods for dose content uniformity and aerodynamic particle size distribution (APSD) evaluate the Dose 60+X, the last dose before device lockout, for each inhaler besides Dose 1 and Dose 30. This has provided valuable characterization data to assess dose content uniformity and aerodynamic particle size distribution throughout the inhaler life stages. However, for routine quality control of commercial batches, revise the methods to define the end dose as Dose 60, which is your labeled total number of doses, to ensure that consistent analytical methods apply to each tested inhaler. Revise the methods PRD-TM-ANL-00484, PRD-TM-ANL-00482, and PRD-TM-ANL-00412 accordingly.

3. Revise the APSD specification for the drug product to specify which (beginning, middle or end) mean values should meet the acceptance criteria set for the different groupings and fine particle dose. It is our understanding that you intend to set acceptance criteria for the three individual mean values for the three life stages of five inhalers to be tested, i.e.,

mean of beginning doses, mean of middle doses, and mean of end doses. In addition, we request that you set acceptance criteria for each individual determination as well.

4. Based on the data in Table 3.2.P.5.6.6-1, we request that you tighten the mean value acceptance criteria for Group 1 , Group 2 and FPD in the APSD specification of the drug product as follows:
   - Group 1: (b) (4) µg
   - Group 2: (b) (4) µg
   - FPD: (b) (4) µg

5. Considering the "total sum" range of (b) (4) from each determination of APSD for your drug product batches, we request you to set an acceptance criterion of (b) (4) of the claimed delivered dose (375 mcg) for "Total sum (each determination)." Revise your specification to read "Total sum (each determination)" and set the acceptance criterion to be (b) (4) of labeled claim (LC).

6. We note differences (lower results for the middle and end doses) in APSD (Groups 2 and 3) among the beginning, middle, and end doses based on the stability data for the primary stability batches of the drug product. Refer to the Figures 9-29 through 9-40 and Figures 10-29 through 10-40 in your stability report PRD-RPT-ANL-00302. Provide an explanation for these different APSD results through the life of the product, and for the batch to batch differences.

7. Explain why the device does not lock out after a fixed number of doses (e.g. 60 doses). Provide available information to demonstrate the accuracy of the dose indicator, i.e., when "0" (zero) appears in the middle of the dose indicator, it should correspond to the labeled number of doses (60) taken by the patient.

8. Clarify whether the claimed delivered dose (375 mcg) was obtained with an air flow rate of 60 L/min or 65 L/min. The analytical method should specify a defined air flow rate for the test.

9. Specify the number of inhalers distributed to the patients in the clinical study LAS-MD-33 for us to understand the rate of malfunctioning devices.

10. Clarify the orientation of the device in the commercial packaging configuration. The same device storage orientation should be used for the post approval drug product stability studies.

11. We remind you that the Master Batch Record (Batch Number: Master) submitted for the drug product contains errors in the calculation of limits of individual cartridge fill weight for in-process testing (b) (4) operation, Page 3 of 19). In addition, it does not have a (b) (4) formula on Page 1 of 17 under (b) (4). Submit an updated master batch record.

If you have any questions, call Swati Patwardhan, Regulatory Project Manager-Quality, at 301-796-4085.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

PRASAD PERI
02/16/2012

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: February 7, 2012

To: Dr. Amjad Iqbal Associate Director	**From:** CDR Sadaf Nabavian Regulatory Project Manager
Company: Forest Laboratories, Inc.	Division of Pulmonary, Allergy and Rheumatology Products
Fax number: 631-858-7921	**Fax number:** 301-796-9728
Phone number: 201-386-2117	**Phone number:** 301-796-2300

Subject: NDA 202-450; Nonclinical Information Request

Total no. of pages including cover: 3

Comments: Please confirm receipt. Thanks.

Document to be mailed: YES xNO

NDA 202450
Aclidinium Bromide
Forest Laboratories, Inc.

Dear Dr. Iqbal:

Your NDA submission dated June 23, 2011, is currently under review and we have the following comments and requests for information:

- For extractables listed in Table 3.2.P.2.4.1.10-1 [Source: Section 3.2.P.2.4, pg. 89-90], states that the Acceptable Daily Intakes (ADIs) based on 60 kg body weight were computed based on literature data. Provide detailed toxicological assessments and literature references that were used to determine the ADI for each extractable. If you already included this information in your submission, provide the specific location in the submission that contains the above information.

Submit your responses to me via telephone facsimile to 301-796-9728 or email at Sadaf.Nabavian@fda.hhs.gov by COB Tuesday, February 14, 2012. Your responses will subsequently need to be submitted officially to the NDA. If you have any questions, please contact Sadaf Nabavian, Senior Regulatory Project Manager, at 301-796-2777.

Drafted: LGrace/02.06.2012 (self-initiated)
TRobison/02.06.2012 (concurred)
SNabavian/02.06.2012
Cleared: LJafari/02.07.2012
Finalized: SNabavian/02.207.2012

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

/s/

SADAF NABAVIAN
02/07/2012

From: Rashid, Nichelle E
Sent: Wednesday, November 23, 2011 8:40 AM
To: 'Iqbal, Amjad'
Cc: Rashid, Nichelle E
Subject: RE: Aclidinium NDA 202450

Good Morning Mr. Iqbal,

That is correct.

Thanks,

Nichelle E. Rashid
Senior Safety Regulatory Project Manager

From: Iqbal, Amjad [mailto:Amjad.Iqbal@frx.com]
Sent: Tuesday, November 22, 2011 1:22 PM
To: Rashid, Nichelle E
Subject: Aclidinium NDA 202450

Dear Ms. Rashid,

Thank for you calling me back regarding my question pertaining to the proposed tradename, (b) (4), for the Aclidinium NDA 202450.

I wanted to confirm with you that, as per your voicemail of November 16, 2011, the Proprietary Name Request Unacceptable Letter from DMEPA dated November 14, 2011, was specifically an objection to the (b) (4)

Kindest regards,

Amjad

_____

Amjad Iqbal, Pharm.D.
Associate Director, Regulatory Affairs
Forest Research Institute
Harborside Financial Center
Plaza V, Suite 1900

Jersey City, NJ 07311
USA
201-386-2117
201-524-9711 (fax)
amjad.iqbal@frx.com

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

/s/

NICHELLE E RASHID
02/07/2012

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: February 06, 2012

To: Dr. Amjad Iqbal Associate Director, Pharm.D.	**From:** CDR Sadaf Nabavian Regulatory Project Manager
Company: Forest Laboratories, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: (631) 858-7921	**Fax number:** 301-796-9728
Phone number: (201) 386-2117	**Phone number:** 301-796-2777

Subject: *NDA 202-450; Clinical Information Request*

Total no. of pages including cover: 3

Comments: Please confirm receipt. Thanks.

Document to be mailed: YES x NO

NDA 202450
Aclidinium Bromide
Forest Laboratories, Inc.

Dear Dr. Iqbal:

Your NDA submission dated June 23, 2011, is currently under review and we have the following comments and requests for information.

- We have some concerns regarding discrepancies between the presentation of data in your Advisory Committee Briefing Document and the presentation in your NDA submission. In a number of instances you have chosen to present your safety data in a substantially different format from that submitted previously for our review. For example, we note your choice to present only Serious Events for the MACE analysis and Cardiac SMQ analysis, which differs from the presentation in the original Integrated Summary of Safety and subsequent amendments. We request clarification of the following:

    1. On page 103 of the Briefing Document, you report n=23 (5.1%) for the overall incidence of non-fatal SAEs among patients treated with 200 μg BID in the Long-term Safety trials. These data differ from those listed in your January 6, 2012, submission (n=26, 5.8%).

    2. On page 103 of the Briefing Document, you report n=24 and n=25 for the incidence of non-fatal SAEs among patients treated with 400 μg BID in the Double-blind Long-term safety and Open-label Long-term Safety trials, respectively. In your January 6, 2012, submission you report n=57 for patients treated with 400 μg BID in the Long-Term Safety trials (Double-blind and Open-label combined).

    3. On page 98 of the Briefing Document, you list "Non-CV" as the adjudication result for Patient 135438005, however, in your original submission dated June 23, 2011, you have listed "Insufficient Data" for the adjudication result.

    4. On page 99 of the Briefing Document, you list "Non-CV" as the adjudication result for Patient 114133006. This is consistent with your original submission dated June 23, 2011, ("Non-CV") but different from a subsequent submission dated October 21, 2011, which lists "Insufficient Data."

    5. Clarify the following statement, "A total of 8 deaths in the Safety Population (occurring more than 30 days after stopping investigational product) were reported: 4 deaths in the BID studies (1 [aclidinium bromide 200 μg], 3 [aclidinium bromide 400 μg])…" (page 96) by providing the patient ID numbers for these deaths.

    6. On page 98 of the Briefing Document, you list 23 days as the duration of duration for patient 114233015, which is consistent with your submission

dated June 23, 2011, but differs from your recent submission dated January 6, 2012.

Submit your responses to me via telephone facsimile to 301-796-9728 or email at Sadaf.Nabavian@fda.hhs.gov by COB Monday, February 13, 2012.Your responses will subsequently need to be submitted officially to the NDA. If you have any questions, please contact Sadaf Nabavian, Senior Regulatory Project Manager, at 301-796-2777.

Drafted By: SNabavian/02.06.12

Cleared By: LJafari/02.06.2012

Finalized By: SNabavian/02.06.2012

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

/s/

SADAF NABAVIAN
02/06/2012

NDA 202450
Aclidinium Bromide
Forest Laboratories, Inc.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: 01-17-2012

To: Dr. Amjad Iqbal Associate Director	From: CDR Sadaf Nabavian Regulatory Project Manager
Company: Forest Laboratories, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 631-858-7921	Fax number: 301-796-9728
Phone number: 201-386-2117	Phone number: 301-796-2300

Subject: NDA 202450; Statistical Information Request

Total no. of pages including cover: 3

Comments: Please confirm receipt. Thanks.

Document to be mailed: **YES** **xNO**

NDA 202450
Aclidinium Bromide
Forest Laboratories, Inc.

Dear Dr. Iqbal:

Your NDA submission dated June 23, 2011, is currently under review and we have the following comments and requests for information:

1. We were not able to replicate the results from the analyses of rate of exacerbations [Source: Section 5.3.5.3.27, pg. 108-109 (Table 3.2.1.9-1)]. Results from our analyses of the rate of exacerbations are presented in Table 1 below. Explain the difference and how you arrived with your results.

Table 1: Reviewer's Exploratory Analysis of COPD exacerbations in three efficacy studies

		Observed Data			**Estimate Rate**		**Treatment Comparison**		
Treatment	N (%) of Subject with ≥1 exac.	Total Number of exac.	Total Exposure (years)	Rate per year	Rate	95%CI	Rate Ratio	95%CI	Nominal p-value
Study M33 (week 12) - All Exacerbations (eCRF)									
Placebo (185)	22 (12)	22	38.4	0.57	0.59	(0.44, 0.80)	--	--	--
AB200 (184)	16 (9)	20	38.7	0.52	0.52	(0.38, 0.71)	0.87	(0.56, 1.36)	0.551
AB400 (190)	12 (6)	13	40.6	0.32	0.33	(0.22, 0.49)	0.56	(0.34, 0.92)	0.023
Study M38a (week 12)- All Exacerbations (eCRF)									
Placebo (182)	19 (10)	20	38.7	0.52	0.52	(0.38, 0.72)	--	--	--
AB200 (182)	14 (8)	15	38.8	0.39	0.38	(0.26, 0.55)	0.73	(0.45, 1.19)	0.213
AB400 (177)	19 (11)	21	37.6	0.56	0.53	(0.38, 0.72)	1.01	(0.64, 1.58)	0.973
Study M34 (week 24) - All Exacerbations (eCRF)									
Placebo (273)	56 (21)	62	113.5	0.55	0.59	(0.48, 0.74)	--	--	--
AB200 (277)	44 (16)	48	121.7	0.39	0.43	(0.33, 0.55)	0.72	(0.52, 0.99)	0.047
AB400 (269)	38 (14)	45	120.1	0.37	0.40	(0.31, 0.52)	0.68	(0.49, 0.94)	0.021
Study M34 (week 24) - All Exacerbation (EXACT-PRO)									
Placebo (273)	100 (37)	148	113.5	1.30	1.38	(1.15, 1.66)	--	--	--
AB200 (277)	83 (30)	115	121.7	0.94	1.00	(0.81, 1.23)	0.72	(0.55, 0.94)	0.017
AB400 (269)	78 (29)	111	120.1	0.92	0.98	(0.79, 1.21)	0.71	(0.54, 0.93)	0.012
Study M33 - Moderate or Severe Exacerbation (eCRF)									
Placebo (185)	16 (9)	16	38.4	0.42	0.43	(0.31, 0.58)	--	--	--
AB200 (184)	12 (7)	12	38.7	0.31	0.32	(0.22, 0.45)	0.74	(0.46, 1.19)	0.217
AB400 (190)	11 (6)	11	40.6	0.27	0.28	(0.19, 0.41)	0.66	(0.41, 1.06)	0.086
Study M38a - Moderate or Severe Exacerbation (eCRF)									
Placebo (182)	19 (10)	19	38.7	0.49	0.50	(0.37, 0.68)	--	--	--
AB200 (182)	11 (6)	11	38.8	0.28	0.28	(0.19, 0.42)	0.57	(0.34, 0.93)	0.026
AB400 (177)	16 (9)	16	37.6	0.43	0.41	(0.29, 0.57)	0.81	(0.51, 1.28)	0.365
Study M34 (week 24) - Moderate or Severe Exacerbation (eCRF)									
Placebo (273)	43 (16)	47	113.5	0.41	0.46	(0.37, 0.58)	--	--	--
AB200 (277)	35 (13)	38	121.7	0.31	0.34	(0.26, 0.44)	0.74	(0.53, 1.04)	0.084
AB400 (269)	33 (12)	38	120.1	0.32	0.34	(0.26, 0.44)	0.74	(0.53, 1.04)	0.084

2. Provide the number needed to treat (NNT) over one year to prevent one COPD exacerbation with 95% confidence interval and include these numbers in the Table.

Submit your responses to me via telephone facsimile to 301-796-9728 or email at Sadaf.Nabavian@fda.hhs.gov by COB Thursday, January 19, 2012 .Your responses will subsequently need to be submitted officially to the NDA. If you have any questions, please contact Sadaf Nabavian, Senior Regulatory Project Manager, at 301-796-2777.

NDA 202450
Aclidinium Bromide
Forest Laboratories, Inc.

Initiated by: Feng Zhou/01.17.12 (self-initiated)
JBuenconsejo/01.17.12 (concurred)
SNabavian/01.12.2012 (minor edits)

Cleared by: LJafari/01.17.2012

Finalized by: SNabavian/01.17.2012

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

/s/

SADAF NABAVIAN
01/17/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202450

METHODS VALIDATION
MATERIALS RECEIVED

Forest Laboratories
Attention: Amjad M. Iqbai
Harborside Financial Center
Plaza V, Suite 1900
Jersey City, NY 07311

Dear Amjad M. Iqbai:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Aclidinium Bromide dry Powder Inhaler, 400 mcg and to our 12/21/2011, letter requesting sample materials for methods validation testing.

We acknowledge receipt on 1/11/2012, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

James F. Allgire
Team Leader
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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

/s/

JAMES F ALLGIRE
01/12/2012

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: January 11, 2012

To: Dr. Amjad Iqbal Associate Director, Pharm.D.	**From:** CDR Sadaf Nabavian Regulatory Project Manager
Company: Forest Laboratories, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: (631) 858-7921	**Fax number:** 301-796-9728
Phone number: (201) 386-2117	**Phone number:** 301-796-2777

Subject: *NDA 202-450; OSE Information Request*

Total no. of pages including cover: 3

Comments: Please confirm receipt. Thanks.

Document to be mailed: YES x NO

NDA 202450
Aclidinium Bromide
Forest Laboratories, Inc.

Dear Dr. Iqbal:

Your NDA submission dated June 23, 2011, is currently under review and we have the following requests for information:

1. What is the difference between the EEP Professional Samples (60 actuations) and the other Professional Samples (30 actuations) other than the number of actuations? Do you anticipate different distribution channels for the two different professional samples? If so, provide details.

2. Provide rationale as to why two types of professional samples are required.

3. Clarify what is included in the EEP "Kit" other than the 60 actuation inhaler.

4. Will the "Patient Information Instructions for Use Booklet" be packaged in trade cartons, professional sample cartons, and EEP cartons?

5. Clarify the difference between the two EEP carton labeling (carton and outer carton).

6. Provide two samples each of the various packaging configurations (trade, professional sample, and EEP sample) including all carton labeling and co-packaged materials.

Submit your responses to me via telephone facsimile to 301-796-9728 or email at Sadaf.Nabavian@fda.hhs.gov by COB Wednesday, January 18, 2012 .Your responses will subsequently need to be submitted officially to the NDA. If you have any questions, please contact Sadaf Nabavian, Senior Regulatory Project Manager, at 301-796-2777.

Drafted By: SNabavian/01.11.12

Cleared By: LJafari/01.11.12

Finalized By: SNabavian/01.11.12

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

/s/

SADAF NABAVIAN
01/11/2012

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: January 04, 2012

To: Dr. Amjad Iqbal Associate Director, Pharm.D.	**From:** CDR Sadaf Nabavian Regulatory Project Manager
Company: Forest Laboratories, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: (631) 858-7921	**Fax number:** 301-796-9728
Phone number: (201) 386-2117	**Phone number:** 301-796-2777

Subject: *NDA 202-450; Clinical Information Request*

Total no. of pages including cover: 4

Comments: Please confirm receipt. Thanks.

Document to be mailed: YES x NO

Dear Dr. Iqbal:

Your NDA submission dated June 23, 2011, is currently under review and we have the following comments and requests for information:

Provide the following tables outlined below:

- "Any Death," should include all deaths, without any qualifiers or limitations. The Summary of Deaths in Tables 2, 4, 6, and 8 should include all deaths. The term "BID Long-Term Safety Trials" refers only to patients enrolled in Trials LAS-MD-35, LAS-MD-36, and LAS-MD-38 Part B, i.e., patients who were in the lead-in trials (LAS-MD-33 or LAS-MD-38 Part A) but who did not roll over into the extension trials (LAS-36 or LAS-MD-38 Part B) should be excluded from the "BID Long-Term Safety Trials" pooled group.

Table 1. Incidence of Death: BID Placebo-Controlled Trials (BID Group 1A), Safety Population

	Placebo N= ET=		**Aclidinium 200 µg N= ET=**		**Aclidinium 400 µg N= ET=**	
	n (%)	Incidence Rate	n (%)	Incidence Rate	n (%)	Incidence Rate
On-Treatment Death						
Any Death						

Table 2. Summary of Deaths: BID Placebo-Controlled Trials (BID Group 1A), Safety Population

Trial ID	**Patient ID**	**Age/Sex**	**Duration of Treatment**	**Time to Death**	**On-Treatment (Yes/No)**	**Cause of Death PT**
Placebo						
Aclidinium 200 µg						
Aclidinium 400 µg						

Table 3. Incidence of Death: BID Long-Term Safety Trials, Safety Population, ISS

	Aclidinium 200 µg N=448 ET=293.5		Aclidinium 400 µg N=891 ET=507.4	
	n (%)	Incidence Rate	n (%)	Incidence Rate
On-Treatment Death				
Any Death				

Table 4. Summary of Deaths: BID Long-Term Safety Trials, Safety Population, ISS

Trial ID	Patient ID	Age/Sex	Duration of Treatment	Time to Death	On-Treatment (Yes/No)	Cause of Death PT
Aclidinium 200 µg						
Aclidinium 400 µg						

Table 5. Incidence of Death: BID Long-Term Safety Trials, Safety Population, 120-Day Safety Update

	Aclidinium 200 µg N=448 ET=362.2		Aclidinium 400 µg N=891 ET=738.7	
	n (%)	Incidence Rate	n (%)	Incidence Rate
On-Treatment Death				
Any Death				

Table 6. Summary of Deaths: BID Long-Term Safety Trials, Safety Population, 120-Day Safety Update

Trial ID	Patient ID	Age/Sex	Duration of Treatment	Time to Death	On-Treatment* (Yes/No)	Cause of Death PT
Aclidinium 200 µg						
Aclidinium 400 µg						

Table 7. Incidence of Death: Once-Daily Program (QD Dosing Group 1), Safety Population

	Placebo N=819 ET=357.9		Aclidinium < 200 µg N=201 ET=15.6		Aclidinium 200 µg N=1657 ET=1101.5		Aclidinium > 200 µg N=91 ET=5.3	
	n (%)	Incidence Rate	n (%)	Incidence Rate	n (%)	Incidence Rate	n (%)	Incidence Rate
On-Treatment Death								
Any Death								

Table 8. Summary of Deaths: Once-Daily Program (QD Dosing Group 1), Safety Population

Trial ID	Patient ID	Age/Sex	Duration of Treatment	Time to Death	On-Treatment* (Yes/No)	Cause of Death PT
Placebo						
Aclidinium 200 µg						

Submit your responses to me via telephone facsimile to 301-796-9728 or email at Sadaf.Nabavian@fda.hhs.gov by COB Friday, January 06, 2012 .Your responses will subsequently need to be submitted officially to the NDA. If you have any questions, please contact Sadaf Nabavian, Senior Regulatory Project Manager, at 301-796-2777.

Drafted By: SNabavian/01.04.12

Cleared By: LJafari/01.04.2012

Finalized By: SNabavian/01.04.2012

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

/s/

SADAF NABAVIAN
01/04/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202450

REQUEST FOR METHODS VALIDATION MATERIALS

Forest Laboratories
Attention: Amjad M. Iqbai
Harborside Financial Center
Plaza V, Suite 1900
Jersey City, NY 07311

Dear Amjad M. Iqbai:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Aclidinium bromide dry powder inhaler, 400 mcg.

We will be performing methods validation studies on Aclidinium bromide dry powder inhaler, 400 mcg, as described in NDA 202450

In order to perform the necessary testing, we request the following sample materials and equipments:

Current version of methods;

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

Standards and Samples

1000 mg Aclidinium Bromide Reference Standard
50 Aclidinium Bromide Dry Powder Inhalers

Equipment (The Dose Collection Apparatus, adaptors and HPLC columns will be returned)

(b) (4)

Please include the MSDSs and Certificates of Analysis for the samples and standards.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: James F. Allgire
1114 Market Street, Room 1002
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

James F. Allgire
Team Leader
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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

/s/

JAMES F ALLGIRE
12/21/2011

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: December 05, 2011

To: Dr. Amjad Iqbal Associate Director, Pharm.D.	**From:** CDR Sadaf Nabavian Regulatory Project Manager
Company: Forest Laboratories, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: (631) 858-7921	**Fax number:** 301-796-9728
Phone number: (201) 386-2117	**Phone number:** 301-796-2777

Subject: *NDA 202-450; Clinical Information Request*

Total no. of pages including cover: 16

Comments: Please confirm receipt. Thanks.

Document to be mailed: **YES** **x NO**

Dear Dr. Iqbal:

Your NDA submission dated June 23, 2011, is currently under review and we have the following comments and requests for information:

Provide the tables outlined below, noting the following:

- The term "BID Long-Term Safety Trials" refers only to patients enrolled in Trials LAS-MD-35, LAS-MD 36, and LAS-MD-38 Part B, i.e., patients who were in the lead-in trials (LAS-MD-33 or LAS-MD-38 Part A) but who did not roll over into the extension trials (LAS-36 or LAS-MD-38 Part B) should be excluded from the "BID Long-Term Safety Trials" pooled group.

- Provide the derivation of "N" for each treatment group (200 μg and 400 μg) comprising the "BID Long-Term Safety Trials" pooled group (i.e., explain the number of patients that each individual trial contributes to the overall pooled group). Indicate the number of patients included in each treatment arm (200 μg and 400 μg) who previously received an alternative treatment (i.e., placebo or 200 ug) during participation in a lead-in trial.

- When reporting events for the pooled group "BID Long-Term Safety Trials," report only those events taking place during Trials LAS-MD-35, LAS-MD-36, and LAS-MD-38 Part B. For example, if a patient enrolled in Trial LAS-MD-33 who subsequently enrolls in Trial LAS-MD-36 experiences a nonfatal SAE while in Trial LAS-MD-33, that event should be reported for BID Group 1A, but not for the "BID Long-Term Safety Trials" pooled group.

Table 1. Subject Disposition: BID Placebo-Controlled Trials (BID Group 1A)

Disposition	Placebo	Aclidinium 200 µg	Aclidinium 400 µg
All Randomized Subjects (N)			
Number of Subjects who Completed, n (%)			
Number of Subjects who Discontinued, n (%)			
Primary Reason for Discontinuation, n (%)			
Adverse Event			
Abnormal Test Result			
Treatment Failure			
Protocol Violation			
Noncompliance			
Subject Withdrew Consent			
Lost to Follow- up			
Administrative Problem			
Other			
Safety Population, n (%)			
ITT Population, n (%)			
PP Population, n (%)			

Note: Calculate percentages based on all randomized subjects shown in the same column.

Table 2. Subject Disposition: BID Long-Term Safety Trials, ISS

Disposition	Aclidinium 200 µg	Aclidinium 400 µg
All Randomized (N)		
Number of Subjects who Completed, n (%)		
Number of Subjects who Discontinued, n(%)		
Primary Reason for Discontinuation, n (%)		
Adverse Event		
Abnormal Test Result		
Treatment Failure		
Protocol Violation		
Noncompliance		
Subject Withdrew Consent		
Lost to Follow- up		
Administrative Problem		
Other		
Safety Population, n (%)		
ITT Population, n (%)		
PP Population, n (%)		

Note: Calculate percentages based on all randomized subjects shown in the same column.

Table 3. Subject Disposition: BID Long-Term Safety Trials, 120-Day Safety Update

Disposition	Aclidinium 200 µg	Aclidinium 400 µg
All Randomized (N)		
Number of Subjects who Completed, n (%)		
Number of Subjects who Discontinued, n (%)		
Primary Reason for Discontinuation, n (%)		
Adverse Event		
Abnormal Test Result		
Treatment Failure		
Protocol Violation		
Noncompliance		
Subject Withdrew Consent		
Lost to Follow- up		
Administrative Problem		
Other		
Safety Population, n (%)		
ITT Population, n (%)		
PP Population, n (%)		

Note: Calculate percentages based on all randomized subjects shown in the same column.

Table 4. Demographics and Other Baseline Characteristics: BID Long-Term Safety Trials, Safety Population

Characteristic	Aclidinium 200 µg N=	Aclidinium 400 µg N=
Age, year		
Mean (SD)		
Median		
Min, Max		
Sex, n (%)		
Female		
Male		
Race, n (%)		
White		
Black or African American		
Asian		
American Indian or Alaskan Native		
Other		
Body Mass Index (kg/m^2)		
Mean (SD)		
Min, Max		
Severity of COPD		
Mild/Moderate		
Severe/Very Severe		
Missing		
Smoking Status		
Current smoker		
Ex-smoker		

Table 5. Incidence of Death: BID Placebo-Controlled Trials (BID Group 1A), Safety Population

	Placebo N=		Aclidinium 200 µg N=		Aclidinium 400 µg N=	
	n (%)	Incidence Rate	n (%)	Incidence Rate	n (%)	Incidence Rate
On-Treatment Death*						
Any Death						

*Provide definition of On-Treatment Death

Table 6. Summary of All Deaths: BID Placebo-Controlled Trials (BID Group 1A), Safety Population

Trial ID	Patient ID	Age/Sex	Duration of Treatment	Time to Death	On-Treatment* (Yes/No)	Cause of Death PT
Placebo						
Aclidinium 200 µg						
Aclidinium 400 µg						

*Provide definition of On-Treatment Death

Table 7. Incidence of Death: BID Long-Term Safety Trials, Safety Population, ISS

	Aclidinium 200 µg N=		Aclidinium 400 µg N=	
	n (%)	Incidence Rate	n (%)	Incidence Rate
On-Treatment Death*				
Any Death				

*Provide definition of On-Treatment Death

Table 8. Summary of Deaths: BID Long-Term Safety Trials, Safety Population, ISS

Trial ID	Patient ID	Age/Sex	Duration of Treatment	Time to Death	On-Treatment* (Yes/No)	Cause of Death PT
Aclidinium 200 µg						
Aclidinium 400 µg						

*Provide definition of On-Treatment Death

Table 9. Incidence of Death: BID Long-Term Safety Trials, Safety Population, 120-Day Safety Update

	Aclidinium 200 µg N=		Aclidinium 400 µg N=	
	n (%)	Incidence Rate	n (%)	Incidence Rate
On-Treatment Death*				
Any Death				

*Provide definition of On-Treatment Death

Table 10. Summary of Deaths: BID Long-Term Safety Trials, Safety Population, 120-Day Safety Update

Trial ID	Patient ID	Age/Sex	Duration of Treatment	Time to Death	On-Treatment* (Yes/No)	Cause of Death PT
Aclidinium 200 µg						
Aclidinium 400 µg						

*Provide definition of On-Treatment Death

Table 11. Incidence of Death: Once-Daily Program (QD Dosing Group 1), Safety Population

	Placebo N=		Aclidinium < 200 µg N=		Aclidinium 200 µg N=		Aclidinium > 200 µg N=	
	n (%)	Incidence Rate	n (%)	Incidence Rate	n (%)	Incidence Rate	n (%)	Incidence Rate
On-Treatment Death*								
Any Death								

*Provide definition of On-Treatment Death

Table 12. Summary of All Deaths: Once-Daily Program (QD Dosing Group 1), Safety Population

Trial ID	Patient ID	Age/Sex	Duration of Treatment	Time to Death	On-Treatment* (Yes/No)	Cause of Death PT
Placebo						
Aclidinium < 200 µg						
Aclidinium 200 µg						
Aclidinium > 200 µg						

*Provide definition of On-Treatment Death

Table 13. Overall Incidence of Non-fatal SAEs and Incidence of Non-fatal SAEs by Preferred Term in ≥ 2 Patients in Any Treatment Group: BID Placebo-Controlled Trials (BID Group 1A), Safety Population

	Placebo N=		Aclidinium 200 µg N=		Aclidinium 400 µg N=	
	n (%)	Incidence Rate	n (%)	Incidence Rate	n (%)	Incidence Rate
Any SAE						
PT						
PT						
PT, etc.						

Table 14. Overall Incidence of Non-fatal SAEs and Incidence of Non-fatal SAEs by Preferred Term in ≥ 2 Patients in Any Treatment Group: BID Long-Term Safety Trials, Safety Population, ISS

	Aclidinium 200 µg N=		Aclidinium 400 µg N=	
	n (%)	Incidence Rate	n (%)	Incidence Rate
Any SAE				
PT				
PT				
PT, etc.				

Table 15. Overall Incidence of Non-fatal SAEs and Incidence of Non-fatal SAEs by Preferred Term in ≥ 2 Patients in Any Treatment Group: BID Long-Term Safety Trials, Safety Population, 120-Day Safety Update

	Aclidinium 200 µg N=		Aclidinium 400 µg N=	
	n (%)	Incidence Rate	n (%)	Incidence Rate
Any SAE				
PT				
PT				
PT, etc.				

Table 16. Overall Incidence of Non-fatal SAEs and Incidence of Non-fatal SAEs by Preferred Term in ≥ 2 Patients in Any Treatment Group: Once-Daily Program (QD Dosing Group 1), Safety Population

	Placebo N=		Aclidinium < 200 µg N=		Aclidinium 200 µg N=		Aclidinium > 200 µg N=	
	n (%)	Incidence Rate	n (%)	Incidence Rate	n (%)	Incidence Rate	n (%)	Incidence Rate
Any SAE								
PT								
PT								
PT, etc.								

Table 17. Incidence of AEs Leading to Dropout: BID Placebo-Controlled Trials (BID Group 1A), Safety Population

	Placebo N=		Aclidinium 200 µg N=		Aclidinium 400 µg N=	
	n (%)	Incidence Rate	n (%)	Incidence Rate	n (%)	Incidence Rate
Patients with any non-fatal AE associated with trial discontinuation, n (%)						

Table 18. Summary of AEs Leading to Dropout: Placebo-controlled Trials, Twice-Daily Program (BID Group 1A), Safety Population

System Organ Class *High Level Term* Preferred Term	Placebo N=		Aclidinium 200 µg N=		Aclidinium 400 µg N=	
	n (%)	Incidence Rate	n (%)	Incidence Rate	n (%)	Incidence Rate
System Organ Class						
High Level Term						
Preferred Term, etc.						

Table 19. Incidence of AEs Leading to Dropout: BID Long-Term Safety Trials, Safety Population, ISS

	Aclidinium 200 µg N=		Aclidinium 400 µg N=	
	n (%)	Incidence Rate	n (%)	Incidence Rate
Patients with any non-fatal AE associated with trial discontinuation, n (%)				

Table 20. Summary of AEs Leading to Dropout: BID Long-Term Safety Trials, Safety Population, ISS

System Organ Class *High Level Term* Preferred Term	Aclidinium 200 µg N=		Aclidinium 400 µg N=	
	n (%)	Incidence Rate	n (%)	Incidence Rate
System Organ Class				
High Level Term				
Preferred Term, etc.				

Table 21. Incidence of AEs Leading to Dropout: BID Long-Term Safety Trials, Safety Population, 120-Day Safety Update

	Aclidinium 200 µg N=		Aclidinium 400 µg N=	
	n (%)	Incidence Rate	n (%)	Incidence Rate
Patients with any non-fatal AE associated with trial discontinuation, n (%)				

Table 22. Summary of AEs Leading to Dropout: BID Long-Term Safety Trials, Safety Population, 120-Day Safety Update

System Organ Class *High Level Term* Preferred Term	**Aclidinium 200 µg N=**		**Aclidinium 400 µg N=**	
	n (%)	Incidence Rate	n (%)	Incidence Rate
System Organ Class				
High Level Term				
Preferred Term, etc.				

Table 23. MACE Score: BID Placebo-Controlled Trials (BID Group 1A), Safety Population

	Placebo N=		**Aclidinium 200 µg N=**		**Aclidinium 400 µg N=**	
	n (%)	Incidence Rate	n (%)	Incidence Rate	n (%)	Incidence Rate
MACE Score						
CV Death						
Non-fatal myocardial infarction						
Non-fatal stroke						

Table 24. Mace Score: BID Long-Term Safety Trials, Safety Population, ISS

	Aclidinium 200 µg N=		**Aclidinium 400 µg N=**	
	n (%)	Incidence Rate	n (%)	Incidence Rate
MACE Score				
CV Death				
Non-fatal myocardial infarction				
Non-fatal stroke				

Table 25. Mace Score: BID Long-Term Safety Trials, Safety Population, 120-Day Safety Update

	Aclidinium 200 µg N=		**Aclidinium 400 µg N=**	
	n (%)	Incidence Rate	n (%)	Incidence Rate
MACE Score				
CV Death				
Non-fatal myocardial infarction				
Non-fatal stroke				

Table 26. Cardiovascular SMQ Results: BID Placebo-Controlled Trials (BID Group 1A), Safety Population

SMQ Category	Placebo N=		Aclidinium 200 µg N=		Aclidinium 400 µg N=	
	n (%)	Incidence Rate	n (%)	Incidence Rate	n (%)	Incidence Rate
Ischemic Heart Disease						
Myocardial infarction						
Other ischemic heart disease						
Supraventricular tachyarrhythmias						
Bradyarrhythmia/conduction defects/sinus node disorders						
Cardiac failure						

Table 27. Cardiovascular SMQ Results: BID Long-Term Safety Trials, Safety Population, ISS

SMQ Category	Aclidinium 200 µg N=		Aclidinium 400 µg N=	
	n (%)	Incidence Rate	n (%)	Incidence Rate
Ischemic Heart Disease				
Myocardial infarction				
Other ischemic heart disease				
Supraventricular tachyarrhythmias				
Bradyarrhythmia/conduction defects/sinus node disorders				
Cardiac failure				

Table 28. Cardiovascular SMQ Results: BID Long-Term Safety Trials, Safety Population, 120-Day Safety Update

SMQ Category	Aclidinium 200 µg N=		Aclidinium 400 µg N=	
	n (%)	Incidence Rate	n (%)	Incidence Rate
Ischemic Heart Disease				
Myocardial infarction				
Other ischemic heart disease				
Supraventricular tachyarrhythmias				
Bradyarrhythmia/conduction defects/sinus node disorders				
Cardiac failure				

Table 29. Cerebrovascular SMQ Results: BID Placebo-Controlled Trials (BID Group 1A), Safety Population

	Placebo N=		Aclidinium 200 µg N=		Aclidinium 400 µg N=	
	n (%)	Incidence Rate	n (%)	Incidence Rate	n (%)	Incidence Rate
Patients with SMQ: central nervous system hemorrhages and cerebrovascular conditions						

Table 30. Cerebrovascular SMQ Results: BID Long-Term Safety Trials, Safety Population, ISS

	Aclidinium 200 µg N=		Aclidinium 400 µg N=	
	n (%)	Incidence Rate	n (%)	Incidence Rate
Patients with SMQ: central nervous system hemorrhages and cerebrovascular conditions				

Table 31. Cerebrovascular SMQ Results: BID Long-Term Safety Trials, Safety Population, 120-Day Safety Update

	Aclidinium 200 µg N=		Aclidinium 400 µg N=	
	n (%)	Incidence Rate	n (%)	Incidence Rate
Patients with SMQ: central nervous system hemorrhages and cerebrovascular conditions				

Table 32. Pneumonia Preferred Term Analysis Results: BID Placebo-Controlled Trials (BID Group 1A), Safety Population

	Placebo N=		Aclidinium 200 µg N=		Aclidinium 400 µg N=	
	n (%)	Incidence Rate	n (%)	Incidence Rate	n (%)	Incidence Rate
Patients with at least 1 pneumonia-related TEAE						

Table 33. Pneumonia Preferred Term Analysis Results: BID Long-Term Safety Trials, Safety Population, ISS

	Aclidinium 200 µg N=		Aclidinium 400 µg N=	
	n (%)	Incidence Rate	n (%)	Incidence Rate
Patients with at least 1 pneumonia-related TEAE				

Table 34. Pneumonia Preferred Term Analysis Results: BID Long-Term Safety Trials, Safety Population, 120-Day Safety Update

	Aclidinium 200 µg N=		Aclidinium 400 µg N=	
	n (%)	Incidence Rate	n (%)	Incidence Rate
Patients with at least 1 pneumonia-related TEAE				

Table 35. TEAEs consistent with Anticholinergic Syndrome: BID Placebo-Controlled Trials (BID Group 1A), Safety Population

	Placebo N=		Aclidinium 200 µg N=		Aclidinium 400 µg N=	
Gastrointestinal disorders	n (%)	Incidence Rate	n (%)	Incidence Rate	n (%)	Incidence Rate
PT						
PT, etc.						
Renal and urinary disorders						
PT						
PT, etc.						
Cardiovascular disorders						
PT						
PT, etc.						
Eye Disorders						
PT						
PT, etc.						
Other disorders						
PT						
PT, etc.						

Table 36. TEAEs consistent with Anticholinergic Syndrome: BID Long-Term Safety Trials, Safety Population, ISS

	Aclidinium 200 µg N=		Aclidinium 400 µg N=	
Gastrointestinal disorders	n (%)	Incidence Rate	n (%)	Incidence Rate
PT				
PT, etc.				
Renal and urinary disorders				
PT				
PT, etc.				
Cardiovascular disorders				
PT				
PT, etc.				
Eye Disorders				
PT				
PT, etc.				
Other disorders				
PT				
PT, etc.				

Table 37. TEAEs consistent with Anticholinergic Syndrome: BID Long-Term Safety Trials, Safety Population, 120-Day Safety Update

	Aclidinium 200 µg N=		Aclidinium 400 µg N=	
Gastrointestinal disorders	n (%)	Incidence Rate	n (%)	Incidence Rate
PT				
PT, etc.				
Renal and urinary disorders				
PT				
PT, etc.				
Cardiovascular disorders				
PT				
PT, etc.				
Eye Disorders				
PT				
PT, etc.				
Other disorders				
PT				
PT, etc.				

Table 38. Intestinal Obstruction-related TEAEs*: BID Placebo-Controlled Trials (BID Group 1A), Safety Population

	Placebo N=		Aclidinium 200 µg N=		Aclidinium 400 µg N=	
	n (%)	Incidence Rate	n (%)	Incidence Rate	n (%)	Incidence Rate
Patients with at least 1 intestinal obstruction-related TEAE						
PT						
PT, etc.						

*Include a footnote describing which preferred terms were assessed as being relevant to the event of interest: intestinal obstruction

Table 39. Intestinal Obstruction-related TEAEs*: BID Long-Term Safety Trials, Safety Population, ISS

	Aclidinium 200 µg N=		Aclidinium 400 µg N=	
	n (%)	Incidence Rate	n (%)	Incidence Rate
Patients with at least 1 intestinal obstruction-related TEAE				
PT				
PT, etc.				

*Include a footnote describing which preferred terms were assessed as being relevant to the event of interest: intestinal obstruction

Table 40. Intestinal Obstruction-related TEAEs*: BID Long-Term Safety Trials, Safety Population, 120-Day Safety Update

	Aclidinium 200 µg N=		Aclidinium 400 µg N=	
	n (%)	Incidence Rate	n (%)	Incidence Rate
Patients with at least 1 intestinal obstruction-related TEAE				
PT				
PT, etc.				

*Include a footnote describing which preferred terms were assessed as being relevant to the event of interest: intestinal obstruction

Table 41. Overall Incidence of TEAEs and Incidence of TEAEs by Preferred Term in ≥ 2% Patients in Any Treatment Group: BID Placebo-Controlled Trials (BID Group 1A), Safety Population

	Placebo N=		Aclidinium 200 µg N=		Aclidinium 400 µg N=	
	n (%)	Incidence Rate	n (%)	Incidence Rate	n (%)	Incidence Rate
Patients with at least 1 TEAE						
PT						
PT, etc.						

Table 42. Overall Incidence of TEAEs and Incidence of TEAEs by Preferred Term in ≥ 2% Patients in Any Treatment Group: BID Long-Term Safety Trials, Safety Population, ISS

	Aclidinium 200 µg N=		Aclidinium 400 µg N=	
	n (%)	Incidence Rate	n (%)	Incidence Rate
Patients with at least 1 TEAE				
PT				
PT				
PT, etc.				

Table 43. Overall Incidence of TEAEs and Incidence of TEAEs by Preferred Term in ≥ 2% Patients in Any Treatment Group: BID Long-Term Safety Trials, Safety Population, 120-Day Safety Update

	Aclidinium 200 µg N=		Aclidinium 400 µg N=	
	n (%)	Incidence Rate	n (%)	Incidence Rate
Patients with at least 1 TEAE				
PT				
PT				
PT, etc.				

Submit your responses to me via telephone facsimile to 301-796-9728 or email at Sadaf.Nabavian@fda.hhs.gov by COB Monday, December 12, 2011 .Your responses will subsequently need to be submitted officially to the NDA. If you have any questions, please contact Sadaf Nabavian, Senior Regulatory Project Manager, at 301-796-2777.

Drafted By: SNabavian/12.05.2011

Cleared By: LJafari/12.05.2011

Finalized By: SNabavian/12.05.2011

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

/s/

SADAF NABAVIAN
12/05/2011

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Monday, November 21, 2011 10:43 AM
To: 'Watts, Jane'
Cc: Iqbal, Amjad; Burrell, Blake
Subject: RE: NDA 202-450-IR

Dear Ms. Watts,
We are reviewing microbiology section of your pending application NDA 202-450 and have following information request.

- **Provide the results of verification studies for the microbial enumeration tests demonstrating that the proposed methods are suitable for use with the drug product**

Please acknowledge the receipt and provide a response by December 5, 2011. In addition a response via email to me will help expedite the review process.

Let me know if you have any question or concern.

Thank you

Swati Patwardhan
Regulatory Health Project Manager for Quality
Office of New Drug Quality Assessment (ONDQA)
Center of New Drug Evaluation and Research
Phone: 301-796-4085
Fax: 301-796-9748

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

/s/

SWATI A PATWARDHAN
11/21/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 202450

PROPRIETARY NAME REQUEST
UNACCEPTABLE

Forest Laboratories, Inc.
Harborside Financial Center
Plaza V, Suite 1900
Jersey City, New Jersey 07311

ATTENTION: Amjad M. Iqbal, PharmD
Associate Director, Regulatory Affairs

Dear Dr. Iqbal:

Please refer to your New Drug Application (NDA) dated June 23, 2011, received June 23, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aclidinium Bromide for Inhalation, 400 mcg per actuation.

We also refer to your August 17, 2011, correspondence, received August 17, 2011, requesting review of your proposed proprietary name, (b) (4). We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

(b) (4)

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names,* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Sadaf Nabavian, (301) 796-2777.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

CAROL A HOLQUIST
11/14/2011

NDA 202450
Aclidinium Bromide
Forest Laboratories, Inc.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: November 01, 2011

To: Dr. Amjad Iqbal Associate Director, Pharm.D.	**From:** CDR Sadaf Nabavian Regulatory Project Manager
Company: Forest Laboratories, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: (631) 858-7921	**Fax number:** 301-796-9728
Phone number: (201) 386-2117	**Phone number:** 301-796-2777

Subject: *NDA 202-450; Statistical Information Request*

Total no. of pages including cover: 3

Comments: Please confirm receipt. Thanks.

Document to be mailed: **YES** **x NO**

NDA 202450
Aclidinium Bromide
Forest Laboratories, Inc.

Dear Dr. Iqbal:

Your NDA submission dated June 23, 2011, is currently under review and we have the following comment and requests for information:

- We are unable to replicate the results presented in table 3.2.1.9-1 of the Integrated Summary of Efficacy (ISE). Explain the model used to analyze the data, and submit the SAS code used to generate the results. In addition, submit the SAS dataset name and variable names that were used in the analysis.

Submit your responses to me via telephone facsimile to 301-796-9728 or email at Sadaf.Nabavian@fda.hhs.gov by COB Monday, November 07, 2011 .Your responses will subsequently need to be submitted officially to the NDA. If you have any questions, please contact Sadaf Nabavian, Senior Regulatory Project Manager, at 301-796-2777.

Drafted By: SNabavian/11.01.2011

Cleared By: LJafari/11.01.2011

Finalized By: SNabavian/11.01.2011

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

/s/

SADAF NABAVIAN
11/01/2011

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: October 25, 2011

To: Dr. Amjad Iqbal Associate Director, Pharm.D.	**From:** CDR Sadaf Nabavian Regulatory Project Manager
Company: Forest Laboratories, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: (631) 858-7921	**Fax number:** 301-796-9728
Phone number: (201) 386-2117	**Phone number:** 301-796-2777

Subject: *NDA 202-450; Clinical Information Request*

Total no. of pages including cover: 3

Comments: Please confirm receipt. Thanks.

Document to be mailed: **YES** **x NO**

NDA 202450
Aclidinium Bromide
Forest Laboratories, Inc.

Dear Dr. Iqbal:

Your NDA submission dated June 23, 2011, is currently under review and we have the following comment and requests for information:

- We note that in the ISS, BID Group 1B is having N=568 patients who were treated with 200 µg and N=1005 patients who were treated with 400 µg. Provide the origin for these two numbers (i.e. how many unique patients come from each of the trials, by treatment group, comprising BID Group 1B). Provide the same information with any additional submissions including data on BID Group 1B.

Submit your responses to me via telephone facsimile to 301-796-2777 or email at Sadaf.Nabavian@fda.hhs.gov by COB Monday, October 31, 2011 .Your responses will subsequently need to be submitted officially to the NDA. If you have any questions, please contact Sadaf Nabavian, Senior Regulatory Project Manager, at 301-796-2777.

Drafted By: SNabavian/10.25.2011

Cleared By: LJafari/10.25.2011

Finalized By: SNabavian/10.25.2011

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

/s/

SADAF NABAVIAN
10/24/2011

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 06, 2011

TO: Lena Maslov, Pharm.D., Drug Safety Evaluator, DMEPA, OSE

THROUGH : Sadaf Nabavian, Pharm.D., Regulatory Project Manager, DPARP

FROM: Jennifer Pippins, M.D.

SUBJECT: Objection to the proposed proprietary name for aclidinium bromide

APPLICATION/DRUG: NDA 202450 (aclidinium bromide)

The primary reviewer, Dr. Jennifer Pippins, assigned to NDA 202450, aclidinium bromide, has moderate level of concerns regarding the proposed proprietary name, (b) (4) The reviewers comments were conveyed to the safety evaluator from DDMAC, Lena Maslov, and DDMAC will schedule a teleconference with the sponsor to discuss the level of concern from the Division's standpoint.

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

/s/

SADAF NABAVIAN
10/25/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202450 **INFORMATION REQUEST**

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Forest Laboratories, Inc.
Harborside Financial Center
Plaza Five, Suite 1900
Jersey City, NJ 07311

Attention: Amjad M. Iqbal, Pharm.D.
Associate Director, Regulatory Affairs

Dear Dr. Iqbal:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for aclidinium bromide Inhalation Powder.

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by Cetero Research in Houston, Texas (Cetero).[1] The pervasiveness and egregious nature of the violative practices by Cetero has led FDA to have significant concerns that the bioanalytical data generated at Cetero from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or "prep" run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or "prep" runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by Cetero Research in Houston, Texas during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is

[1] These violations include studies conducted by Bioassay Laboratories and BA Research International specific to the Houston, Texas facility.

searching available documentation to determine which NDAs are impacted by the above findings.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by Cetero Research in Houston, Texas during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have any questions, call Christine Chung, Regulatory Project Manager, at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Chief, Project Management Staff
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

SANDRA L BARNES
09/15/2011

NDA 202450
Aclidinium Bromide
Forest Laboratories, Inc.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: September 12, 2011

To: Dr. Amjad Iqbal Associate Director, Pharm.D.	**From:** CDR Sadaf Nabavian
Company: Forest Laboratories, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: (631) 858-7921	**Fax number:** 301-796-9728
Phone number: (201) 386-2117	**Phone number:** 301-796-2777

Subject: *NDA 202-450; DSI Information Request(2)*

Total no. of pages including cover: 3

Comments: Please confirm receipt. Thanks.

Document to be mailed: **YES** **x NO**

NDA 202450
Aclidinium Bromide
Forest Laboratories, Inc.

Your submission dated August 29, 2011, to NDA 202450, is currently under review and we have the following request for information:

1. Submit amended patient data listings for Study M-34273-34. Following the format similar to Study 33 and Study 38A, provide patient disposition of the randomized population in Study M-34273-34. If submitted recently, identify the location of the information mentioned above.

Submit your responses to me via telephone facsimile to 301-796-2777 or email at Sadaf.Nabavian@fda.hhs.gov by COB Wednesday, September 14, 2011 .Your responses will subsequently needs to be submitted officially to the NDA. If you have any questions, please contact Sadaf Nabavian, Senior Regulatory Project Manager, at 301-796-2777.

NDA 202450
Aclidinium Bromide
Forest Laboratories, Inc.

Drafted By: SNabavian/09.09.11

Cleared By: SBarnes/09/09.2011
AOrencia/
TPurohit-Sheth/

Finalized By: SNabavian/

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

/s/

SADAF NABAVIAN
09/12/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202-450

FILING COMMUNICATION

Forest Laboratories, Inc.
Harborside Financial Center
Plaza V, Suite 1900
Jersey City, NJ 07311

Attention: Amjad M. Iqbal, Pharm.D.
Associate Director, Regulatory Affairs

Dear Dr. Iqbal:

Please refer to your New Drug Application (NDA) dated June 23, 2011, received, June 23, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for aclidinium bromide Inhalation Powder

We also refer to your amendments dated August 11, 17, and 29, 2011.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is April 23, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by March 22, 2012.

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

Clinical

1. As stated in the pre-NDA meeting responses dated February 25, 2011, adequate safety data to support the application is expected at the time of NDA filing. We will not be able to conduct a substantive review of information submitted at the 120-day safety update; as a result, this additional data has limited capacity to support a regulatory action. In general, we note that long-term exposure to the proposed 400 mcg BID dose of aclidinium is relatively small. The adequacy of the safety data to support the safety of your product will be a review issue and may impact approvability of the proposed product.

2. We note your proposal to include results from Trial LAS-MD-26 in the label. (b) (4)

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

We also request that you submit the following information:

CMC

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

2. 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.

3. 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.

4. Provide drug product characterization data to demonstrate the effect on the performance (e.g., emitted dose, aerodynamic particle size distribution) of the drug product if the device is horizontal but inverted.

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

6. 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.

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

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

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

9. In the Table of Contents there should be no periods after the numbers for the section and subsection headings.

10. The proprietary and established names can be repeated at the beginning of the Full Prescribing Information (FPI), or at the beginning of each page of the FPI (e.g., as a header), to enhance product identification on subsequent pages of labeling.

11. Add "Patient Information and Instructions for Use" in parenthesis after the statement "*See FDA-approved Patient Labeling"* to Section 17 of the FPI.

We request that you resubmit labeling that addresses these issues by September 23, 2011. The resubmitted labeling will be used for further labeling discussions.

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

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. We acknowledge receipt of your request for a waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Sadaf Nabavian, Regulatory Project Manager, at (301) 796-2777.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology
Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

BADRUL A CHOWDHURY
09/02/2011

NDA 202450
Aclidinium Bromide
Forest Laboratories, Inc.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: August 26, 2011

To: Dr. Amjad Iqbal Associate Director, Pharm.D.	**From:** CDR Sadaf Nabavian
Company: Forest Laboratories, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: (631) 858-7921	**Fax number:** 301-796-9728
Phone number: (201) 386-2117	**Phone number:** 301-796-2777

Subject: *NDA 202-450; DSI Information Request*

Total no. of pages including cover: 3

Comments: Please confirm receipt. Thanks.

Document to be mailed: **YES** **x NO**

NDA 202450
Aclidinium Bromide
Forest Laboratories, Inc.

Your submission dated June 23, 2011, to NDA 202450, is currently under review. We have the following requests for information:

1. For studies 33, 34, and 38 respectively, submit the following patient data listings categorized/organized by clinical investigator site number for all Canadian, German and U.S. sites: (a) randomization scheme, (b) concomitant and prohibited medications, (c) adverse events (including deaths and serious adverse events), (d) protocol deviations/violations, (e) primary efficacy endpoints, and (f) protocol deviations/violations.

2. For all foreign (non-U.S.) sites in studies 33, 34 and 38, respectively, provide the most recent updated principal investigator's name, site number, complete contact address, phone, fax and e-mail.

Submit your responses to me via telephone facsimile to 301-796-2777 or email at Sadaf.Nabavian@fda.hhs.gov by COB Monday, August 29, 2011 .Your responses will subsequently needs to be submitted officially to the NDA. If you have any questions, please contact Sadaf Nabavian, Senior Regulatory Project Manager, at 301-796-2777.

NDA 202450
Aclidinium Bromide
Forest Laboratories, Inc.

Drafted By: SNabavian/08.22.2011

Cleared By: SBarnes/08.25.2011
AOrencia/08.26.2011 (via phone)

Finalized By: SNabavian/08.26.2011

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

/s/

SADAF NABAVIAN
08/26/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202-450

NDA ACKNOWLEDGMENT

Forest Laboratories, Inc.
Harborside Financial Center
Plaza V, Suite 1900
Jersey City, NJ 07311

Attention: Amjad M. Iqbal, Pharm.D.
Associate Director, Regulatory Affairs

Dear Dr. Iqbal:

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

Name of Drug Product: Aclidinium Bromide, Inhalation Powder

Date of Application: June 23, 2011

Date of Receipt: June 23, 2011

Our Reference Number: NDA 202-450

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 22, 2011, in accordance with 21 CFR 314.101(a).

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

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

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

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

If you have any questions, call me at (301) 796-2777.

Sincerely,

{See appended electronic signature page}

Sadaf Nabavian, Pharm.D.
Regulatory Project Manager
Division of Pulmonary, Allergy, and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

SADAF NABAVIAN
07/06/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 68653

MEETING MINUTES

Forest Laboratories
Attention: Charlene R. Ganser, Sr. Manager, Reg. Affairs, CMC
Harborside Financial Center
Plaza V, Suite 1900
Jersey City, New Jersey 07311

Dear Ms. Ganser:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for LAS 34273 Dry Powder Inhaler.

We also refer to the meeting between representatives of your firm and the FDA on January 18, 2011. The purpose of the meeting was to discuss development plan and regulatory strategy intended to support the quality module of the NDA.

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

If you have any questions, call Swati Patwardhan, Regulatory Project Manager at (301) 796-4085.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Acting Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure: meeting minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUG OUALITY ASSESSMENT

Sponsor Name:	Forest Research Institute, Inc.
Application Number:	IND 68653
Product Name:	Aclidinium bromide (LAS34273)
Meeting Requestor:	Charlene R. Ganser, Sr. Manager, Reg. Affairs, CMC
Meeting Type:	Type B
Meeting Category:	Chemistry, Manufacturing and Controls (CMC) Pre-NDA
Meeting Date and Time:	January 18, 2011, 11:00 am to 12:00 pm
Meeting Location:	Food and Drug Administration, White Oak Building 21, Conference Room: 1537 Silver Spring, MD
Received Briefing Package	December 1, 2010
Meeting Chair:	Prasad Peri
Meeting Recorder:	Swati Patwardhan

FDA ATTENDEES:

CENTER OF DRUG EVALUATION AND RESEARCH

Office of New Drug Quality Assessment

Division of New Drug Quality Assessment III:

- Prasad Peri, Ph.D., Acting Branch Chief, Branch VIII
- Alan Schroeder, Ph.D., CMC Lead, Branch VIII
- Craig Bertha, Ph.D., CMC Reviewer, Branch VIII
- Swati Patwardhan, Regulatory Project Manager for Quality, DNDQA III

Office of New Drug Microbiology

- Denise Miller, Microbiologist

Division of Pulmonary, Allergy, and Rheumatology Products

- Banu Karimi-Shah, M. D., Medical Officer
- Timothy Robison, Ph.D., Acting-Team Leader, Pharmacologist

Office of Compliance, Division of Manufacturing and Product Quality

- Vipul Dholakia, Chemist

EXTERNAL ATTENDEES:

Forest Laboratories

- Anil Chhettry, PhD Director, Product Development
- Charlene Ganser, MS Senior Manager, Regulatory Affairs CMC
- Amjad Iqbal, PharmD Associate Director, Regulatory Affairs
- Shashank Mahashabde, PhD VP, Pharmaceutical Research & Development
- Satyam Upadrashta, PhD, RAC Executive Director, Regulatory Affairs CMC
- Terry Martin, DMV, MS, DABDT, DABT Senior Director, Toxicology Almirall, S.A
- Eva Castro CMC-Regulatory Affairs Manager
- Antoni Massó Director of Operations Pharmaceutical Development and CMC Leader Aclidinium
- Carsten Niederlaender Director of Pharmaceutical Development and Site Head, Almirall Sofotec
- Antonio Martinez Tobed, Pre-clinical Consultant for Almirall

1.0 BACKGROUND

- Aclidinium bromide (LAS34273) is being developed for the maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.
- The Pre-NDA CMC meeting was requested to obtain the FDA's concurrence with the regulatory CMC strategy intended to support the quality modules of the NDA.
- Following topics were proposed for discussion and concurrence:

1. Physico-chemical and microbiological specifications for routine control
2. Approach for determination and evaluation of the potential genotoxic impurities

3. Proposed stability data package for the primary NDA registration batches and post-approval stability protocol
4. Suggested stability data package to support the physician sample configuration
5. Physico-chemical and microbiological specifications for routine control at release and stability
6. Study design for leachables.

2.0 DISCUSSION

2.1 Q.1 a

Does the FDA agree with the proposed drug substance NDA specification?

FDA Pre-meeting response:

CMC: The parameters included in the drug substance specification are reasonable. Evaluation of the acceptance criteria will be done at the time of NDA review. We note that you claim to have found (b) (4) of the drug substance. As such, it is important for you to include a description of the (b) (4) that was performed to provide reasonable assurance that there are (b) (4) that could appear later, as it is unknown whether or not the drug substance test parameters would be able to detect the presence of any (b) (4)

Pharmacology/Toxicology: In general, impurity or degradant specifications exceeding qualification thresholds described in the ICH Q3A(R2) and Q3B(R2) Guidances, respectively, should be qualified in nonclinical toxicology studies with duration ≥3 months for chronically administered products. There appear to be inadequate safety margins for the (b) (4) impurity with respect to local toxicity.

Impurities should be qualified with respect to local toxicity in the lung as well as systemic toxicity. Safety with respect to local toxicity in lung is assessed by comparison of animal to human pulmonary deposited doses. Safety with respect to systemic toxicity is assessed by comparison of animal to human AUC values or pulmonary deposited doses.

Use of pulmonary deposited dose: Clinical doses of these impurities and/or degradants should be supported by the animal NOAEL, expressed as the pulmonary deposited dose, with an appropriate safety margin (i.e., 10 rats and 6 for dogs). Analysis of batches used in nonclinical toxicology studies is acceptable assuming that they provide acceptable safety margins. Pulmonary deposited doses should be calculated using deposition factors of 10% for rats, 25% for dogs, and 100% for humans (Toxicologic Testing of Inhaled Pharmaceutical Aerosols" by R.K. Wolff and M.A. Dorato published in Critical Reviews in Toxicology 23(4):343-369, 1993). Safety margins are calculated from the ratios of rat to human or dog to human pulmonary deposited doses.

With respect to local toxicity, exposure to (b) (4) in the 39-week toxicology study with dogs provides an inadequate safety margin (i.e., 0.82) for exposure to this impurity associated with a clinical dose of 400 mcg. Provide justification that

(b) (4) is adequately qualified with respect to local toxicity. Alternatively, conduct an inhalation toxicology study with a minimal duration of 3 months to qualify (b) (4) The NOAEL in this study should provide an acceptable safety margin for clinical exposure to this impurity associated with a dose of 400 mcg.

Safety margins (i.e., 5.3) for (b) (4) and the (b) (4) (b) (4) are marginal although considered acceptable assuming specifications for these impurities are not increased.

Safety margins for specified impurities

Study	Impurity in Batch R001	PDD[1] mcg/kg	Safety margins for impurities in a clinical dose of 200 mcg BID or 400 mcg/day (400/60 = 6.7 mcg/kg)
39-week dog NOAEL = 220 mcg/kg PDD[1] = 55 mcg/kg			(b) (4)
			(b) (4)

Abbreviations: (b) (4) (b) (4)

1. PDD = Pulmonary Deposited Dose

2 (b) (4)

Meeting Discussion:

Forest agreed to submit a description of the polymorph screening data for the drug substance.

According to the Sponsor, no further qualification is required for (b) (4) (b) (4) impurity. In response to the concern expressed by the Agency related to

39-week toxicology study with this impurity providing an inadequate safety margin for local toxicity, Forest referred to PQRI safety threshold for Leachables in Orally Inhaled and Nasal Drug Products (OINDPs), and noted the daily dose of (b) (4) impurity is lower than the threshold of toxicological concern at 1.5 µg/day in the PQRI recommendations. Although (b) (4) is not a leachable, the PQRI recommendations can be referenced as a benchmark, since those recommendations also account for local toxicity (irritation) to the lung

The Sponsor stated that the animal-to-human dose ratio of (b) (4) only accounts for the administered impurity dose, but does not take into account the amount of (b) (4) Data in rats found that (b) (4) of the administered dose in the lungs was (b) (4) (b) (4) For calculation of animal to human dose ratio, Forest claimed that the pulmonary deposited dose of (b) (4) in the dog study was estimated to be (b) (4) which represents a safety margin of (b) (4) with respect to the clinical dose of 800 mcg.

FDA requested that (b) (4) data be submitted in the NDA submission, to which Forest agreed. Forest stated that a draft report was provided in the Annual Report in 2004.

See post-meeting comment in section 3.0.

2.2 **Q. 1b**

Does the Agency concur that sufficient data has been generated to obviate the need for microbial testing on the drug substance?

FDA Pre-meeting response:

Provide the supporting data referred to on p. 24 and in section 10.1.3.3.11.9, in the NDA, for our evaluation to determine if microbial limits and acceptance criteria and testing are necessary for the drug substance.

Meeting Discussion:

Forest agreed to submit the requested supporting data in the NDA submission. No further discussion occurred during the meeting.

2.3 **Q.2**

Does the FDA agree with the Sponsor's evaluation and control strategy of potential genotoxic impurities?

FDA Pre-meeting response:

CMC: You have stated that the (b) (4) were only observed when (b) (4) from a different supplier was used. Include information and/or data that will provide assurance that if the supplier of the starting material changes, this particular potentially genotoxic impurity will not be present in the drug substance produced, as you do not propose routine testing for its absence.

It is stated that the [redacted] As stomach acid contains hydrochloric acid, you will need to provide more specific information in the NDA to justify the absence of any particular controls for this potential genotoxic impurity in the drug substance.

Pharmacology/Toxicology: In general, the control of genotoxic impurities at ≤1.5 mcg/day is acceptable per the Draft Guidance for Industry Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches (December 2008). However, it is noted that levels of structurally-related genotoxic impurities should be summed together and the total should not exceed 1.5 mcg/day (it appears that [redacted] that should be summed together and the total should not exceed 1.5 mcg/day).

Study reports for Ames Salmonella bacterial reverse mutation assays conducted with [redacted] should be provided in the NDA.

The [redacted] should be tested in the bacterial reverse mutation assay as it could potentially form in the stomach acid (see above). Alternatively, provide sufficient justification that potential exposure to this impurity will be ≤1.5 mcg/day.

Meeting Discussion:

In response to issue raised by the Agency in 1st paragraph, Forest agreed to provide a commitment that if a different supplier is used in the future, they will evaluate the [redacted] impurity to confirm potentially genotoxic impurity will not be present in the drug substance produced by that supplier.

Forest claimed that they have done further testing simulating physiological gastric conditions at 37°C for 6 hours. The results showed that the levels of [redacted] were [redacted] equivalent to less than [redacted] The Agency requested that the information related to the simulated testing be submitted in the NDA application, to which Forest agreed.

Per Sponsor, the total sum of the [redacted] was [redacted] and is acceptable per the Draft Guidance for Industry Genotoxic and Carcinogenic Impurities in Drug Substances and Products.

Forest agreed to submit Ames report for [redacted] in the NDA application.

The sponsor reported that the [redacted] was found in significant levels only [redacted]. For a 6-hr incubation in stimulated gastric acid at 37°C, the amount of the [redacted] formed was less than [redacted]. Based upon this information, the Sponsor does not plan to conduct an AMES reverse mutation assay with the [redacted] This will be a review issue when the NDA is submitted.

2.4 Q. 3a

Does the Agency agree that 12 months of stability data from two primary registration batches and nine (9) months of data from the third primary registration batch are adequate to accept the NDA for filing?

FDA Pre-meeting response:

Yes, we agree.

Meeting Discussion:

Forest was satisfied with the preliminary response for this question and no further discussion occurred during the meeting.

2.5 Q.3b

Does the Division agree to accept additional stability data prior to day 120 of the NDA review cycle for review and to appropriately assign the drug product shelf-life?

FDA Pre-meeting response:

Applications should be complete at the time of NDA submission.

We remind you of what we indicated at the May 9, 2009, meeting regarding the inclusion in the application of the statistical analysis for any trending stability parameters and that these analyses should be used to set the proposed expiration dating period.

You may submit updated stability data (with updated statistical analyses and proposed expiry) after the original submission of the NDA, but we can not guarantee that we will be able to review these data and updates during the same review cycle.

Meeting Discussion:

Forest was satisfied with the preliminary response for this question and no further discussion occurred during the meeting.

2.6 Q. 3c

Does the FDA agree that the stability data from the aclidinium bromide inhalation powder batches (b) (4) 400 mcg (60D-30C) configurations are representative to support the stability requirement for the 400 mcg (30D-30C) physician samples, and that it is unnecessary to generate additional stability data for the physician samples?

FDA Pre-meeting Response

Stability data are required for all to-be-marketed configurations and physician samples of new drug products, and expiry periods will be based on the data provided with your application. Although there may be cases where bracketing of strengths may be used to limit the scope of stability studies required for an intermediate strength, this is not typically justified for inhalation powder drug products, where there are a large number of

potential drug-device interactions. [redacted] Therefore, include stability data for the latter 400 mcg configuration if you plan it to be a physician sample.

Meeting Discussion:

Per the Sponsor. [redacted]

FDA did not agree with the Sponsor. [redacted] The Agency would need to have the stability data for the proposed 400 mcg 30D-30C physician sample included in the application. Forest expressed that they plan to file the NDA application in 2nd Quarter of this year and stability study initiation for 400 mcg 30D-30C would delay their projected time line. The Agency agreed that 400 mcg 30D-30C stability data could be submitted later in the NDA cycle. The applicant now proposes to use the 400 mcg 60D-30C configuration as the physician sample and this was agreed upon as a feasible approach. The Agency stated that the applicant could submit the supporting data for the 400 mcg 30D-30C strength later in a supplement for proposed use as a physician sample.

2.7 **Q. 4a**

Does the FDA agree with the proposed drug product NDA specification?

FDA Pre-meeting Response

The specification includes all of the parameters that we would expect to be included for the testing of inhalation powder drug products.

The evaluation of the acceptance criteria will be done at the time of NDA review.

Although you state that you follow the Agency draft guidance regarding the CMC information for support of applications for inhalation powder drug products, provide confirmation that at the time of application submission, data for the mass amount of drug substance found on each accessory and each of the various stages of the [redacted] will be reported, as we requested at the end-of-phase 2 meeting (p. 350 of 654 of the meeting package).

Meeting Discussion:

Forest confirmed that the data for the mass amount of drug substance found on each accessory and each of the various stages of the (b) (4) will be reported in the NDA application and would be presented in the FDA recommended format.

2.8 **Q. 4b**

Does the Agency concur that sufficient data has been generated to discontinue the microbial testing for Escherichia coli and Salmonella in the drug product?

FDA Pre-meeting response:

Yes. If testing for bile tolerant gram negative bacteria is conducted, then it is acceptable for you to drop the specific tests for Escherichia coli and Salmonella in the drug product. The NDA should include the method suitability data supporting the microbial testing performed.

Meeting Discussion:

Forest was satisfied with the preliminary response for this question and no further discussion occurred during the meeting.

2.9 **Q. 4c**

Does the FDA agree with the proposed plan for the leachables study and that no further study is required if no leachable of toxicological concern is detected above the Analytical Evaluation Threshold?

FDA Pre-meeting response:

The safety of leachables/extractables should be addressed as described in the PQRI working group report (i.e., with the AET based on the Safety Concern Threshold (SCT) of 0.15 mcg/day for an individual organic leachable).

Meeting Discussion:

Forest agreed to follow PQRI recommendation. Forest will perform one time study with 12 month sample. If no leachables are identified, no further study will be conducted. FDA agreed to the Forest's proposed strategy.

2.10 **Q. 5a**

Does the FDA concur that the in-vitro data provided satisfactorily demonstrates the equivalency of the DPI devices (60D-30C and 60D-60C) and that the Sponsor has fulfilled the commitment?

FDA Pre-meeting response:

As agreed upon at the end-of-phase 2 meeting (p. 408), these data will be submitted with the NDA. They will be evaluated during review of the NDA.

Provide the APSD data profiles graphically on a stage-by-stage basis (not just group data) such that it will be easy to assess the comparability of the profiles from the first 30 doses (used in trials) to those that would be attained from the last 30 doses from the 60 dose devices (to be available with commercial product).

Meeting Discussion:

Forest agreed to provide the APSD data profiles graphically on a stage-by-stage basis in the NDA application. Forest presented slides during discussion of this question. The slides were an illustration example on how the APSD data will be submitted. The Agency agreed with the proposed presentation format for the APSD data.

2.11 Q. 5b

Does the FDA agree with the proposed approach for testing (b) (4) (b) (4)

FDA Pre-meeting response:

No, we do not agree. We expect you to have a larger number of devices returned and tested for the dose content uniformity and the APSD (not just the fine particle dose), e.g., n = 50 for DCU and 20 for APSD for each strength.

Meeting Discussion:

The Agency indicated that the APSD data should be provided as a complete profile and not just the fine particle fraction. Forest agreed to provide the results as requested.

2.12 Q. 6a.

Does the FDA concur that the Module 3 organization and quality elements are appropriate for the NDA submission?

FDA Pre-meeting Response:

As you have stated that you plan to follow the ICH and FDA guidance documents for formatting the NDA in the CTD format, which is acceptable.

In addition, present a summary of the stability data on a parameter-by-parameter basis, in tabular format. Provide summary graphical plots of the stability data for the most important (e.g., dose content uniformity (DCU), aerodynamic particle size distribution (APSD)) and any trending parameters for each storage condition and position. Include graphs with both mean and individual data. Separate the data for different lots in the graphical data. Include the proposed acceptance criteria limits on the plots (e.g., for DCU, expand this to include limits for ± 15, 20, 25, 30, 35% of label claim).

Meeting Discussion:

Forest was satisfied with the preliminary response for this question and no further discussion occurred during the meeting.

2.13 Q. 7

Does the FDA agree with the Sponsor's position that sufficient number of batches have been manufactured at commercial scale with established in-process controls and that there is no need to conduct additional process validation?

FDA Pre-meeting response:

It is the company's responsibility to conduct all studies necessary to assure that the commercial manufacturing process is capable of consistently delivering quality product. The number of lots included in a study is not a performance criteria.

FDA does not approve process validation approaches, protocols, or specific batches used in process validation studies. The actual protocols, acceptance criteria and study outcomes will be evaluated during an inspection. It is your company's responsibility to conduct all studies necessary to assure your commercial manufacturing process is capable of consistently delivering quality product.

Meeting Discussion:

Forest was satisfied with the preliminary response for this question and no further discussion occurred during the meeting.

3.0 ADDITIONAL COMMENTS

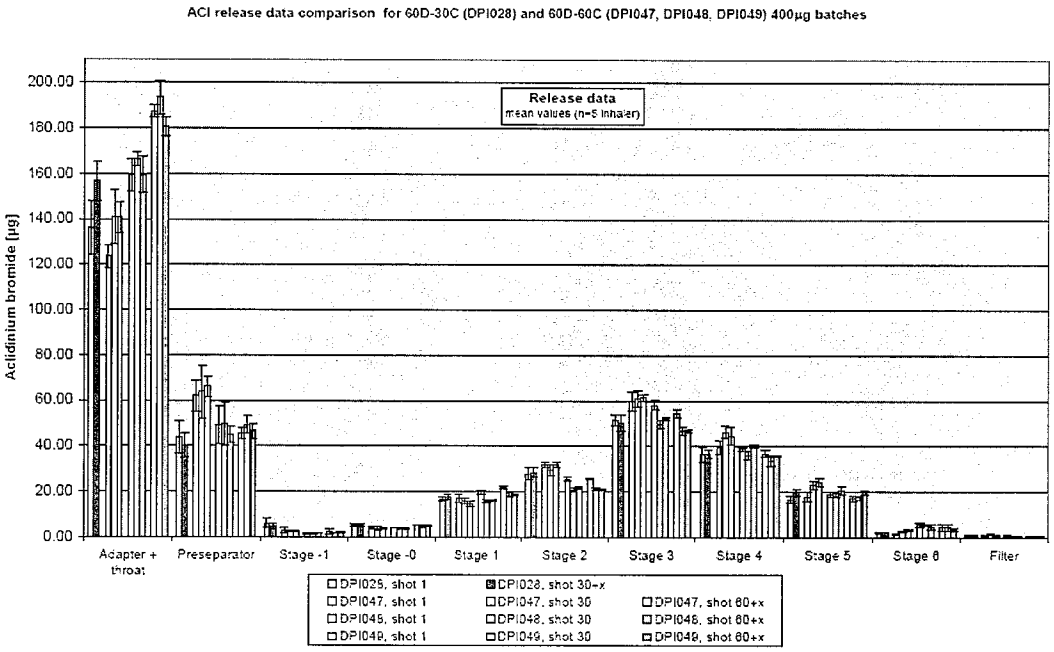
- Forest distributed few placebo samples of the inhaler device and explained the functioning aspect of the device.
- Post Meeting Comment: Under Question 1a, Pharm-Tox calculations of safety margins for impurities were relative to a clinical dose of 400 mcg/day (200 mcg BID). If the final clinical dose should be 800 mcg/day (400 mcg BID), the Sponsor should ensure that there are adequate safety margins (i.e., approximately 10-fold for rats or 6-fold dogs) for impurities. (b) (4) (b) (4) (b) (4) on either a mcg/kg or mcg/gram lung weight basis. Alternatively, provide justification that these impurities are adequately qualified by other nonclinical data (e.g., (b) (4) (b) (4)

4.0 CONCURRENCE:

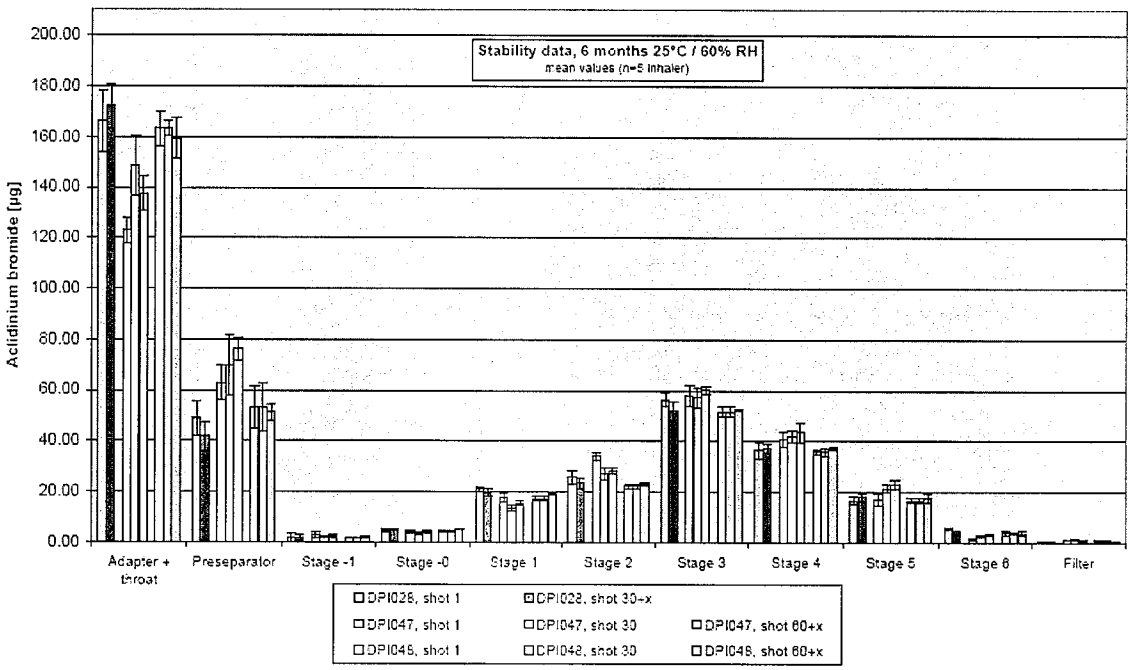
{See appended electronic signature page}

Prasad Peri.
Acting Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment

5.0 ATTACHMENTS AND HANDOUTS



ACI stability data comparison between 60D-30C (DPI028) and 60D-60C (DPI047, DPI048) 400µg batches



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

/s/

PRASAD PERI
02/11/2011

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type:	C
Meeting Category:	CMC
Meeting Date and Time:	May 12, 2009; 1:00 P.M. to 2:00 P.M.
Meeting Location:	Telephone: 1-888-809-4012
Application Number:	IND 68,653
Product Name:	LAS 34273 (aclidinium bromide)
Received Briefing Package	April 14, 2009
Sponsor Name:	Forest Research Institute
Meeting Requestor:	Amjad Iqbal
Meeting Chair:	Craig Bertha
Meeting Recorder:	Eunice Chung

Meeting Attendees:

FDA Attendees

Craig Bertha, Ph.D., CMC Reviewer, Branch II, ONDQA

Prasad Peri, Ph.D., Pharmaceutical Assessment Lead, Branch II, ONDQA

Banu Karimi Shah, M.D., Clinical Reviewer, Division of Pulmonary and Allergy Products

Sally Seymour, M.D., Deputy Director for Safety, Division of Pulmonary and Allergy

Eunice Chung, Pharm.D., Regulatory Project Manager, Division of Pulmonary and Allergy

Sponsor Attendees

Forest Attendees:

Shashank Mahashabde, Vice President, Pharmaceutical Research & Development

Bhaveshkumar Kothari, Sr. Research Scientist, Pharmaceutical Research & Development

Satyam Upadrashta, Executive Director, Regulatory Affairs CMC

Amjad Iqbal, Assistant Director, Regulatory Affairs

Linda Kunka, Manager, Regulatory Affairs

Carol Satler, Vice President, Pulmonary and Cardiovascular Clinical Development

Cynthia F. Caracta, MD, FCCP, Director, Clinical Development

Almirall Attendees:

Carsten Niederlaender, Director of Pharmaceutical Development and Site Head Almirall Sofotec

Antoni Massó, Director of Pharmaceutical Development Operations

Paul Crick, Head of CMC Regulatory Affairs

Eva Castro, CMC Regulatory Affairs Manager

Thomas Pieper, Group Leader for Late Phase Development

Esther Garcia Gil, Global Clinical Leader

BACKGROUND

Dr. Amjad Iqbal of Forest Research Institute, sent a correspondence, dated February 19, 2009, requesting a Type C CMC meeting to discuss the ongoing development of the aclidinium bromide drug product. The briefing package with questions (***bold italics***) to the Agency was received on April 14, 2009. Preliminary comments (in *italics*) were faxed to the sponsor on May 8, 2009. Upon review of the Division's responses, Forest decided that a face-to-face to meeting was not warranted and requested that the meeting be converted to a teleconference to seek clarification on the Division's responses to Questions 6a, 7a, and 8a. Forest's Position regarding the Division's responses to these questions are in **bold normal font**. Forest also included information relating to questions 1b, 4, and the Division's "Additional Comment" that was solely for informational purposes only. Any discussion during the March 27, 2009, meeting is in normal font.

QUESTIONS, RESPONSES, AND DISCUSSION

Question 1a: PSD Specification: Does the FDA agree that in-vitro data could be used to support revision of the particle size acceptance criteria for the API?

Division Response:

It is reasonable to use the in vitro aerodynamic particle size distribution (APSD) data observed for the drug product used in the clinical trials to help set the appropriate particle size distribution (PSD) criteria for the drug substance, assuming safety and efficacy are established by these trials and that you establish an APSD/PSD correlation. See the response to 1.b below.

Discussion:

No Discussion Required

Question 1b: PSD Specification: Does the FDA concur with the revised particle size specification proposed for the drug substance?

Division Response:

A review of the drug substance PSD data and evaluation of the associated acceptance criteria will be done during the NDA review in the context of all supporting CMC data. The acceptance criteria for the PSD of the drug substance should reflect the data for those batches that were used to prepare the clinical trial drug product. Establishing comparability of the clinical trial drug product to that which will be manufactured for commercial distribution will be a main consideration regarding your proposed acceptance criteria (drug substance, drug product, excipients, etc.).

Although your PSD/APSD data appear to demonstrate a correlation, our evaluation of the proposed acceptance criteria will also take into consideration the ranges of data

collected during testing to specification for the components used to prepare the clinical drug product, and for the clinical trial drug product itself, when evaluating the acceptance criteria for these components and for the drug product.

Regarding the proposed acceptance criteria for the APSD groups in table 1-5, the Agency generally recommends ranges that do not exceed two fold, particularly for those particles that are in the respirable size range. Data presented in the NDA should be presented both in terms of the proposed groups as well as on a stage-by-stage basis.

Sponsor Position:

The information presented below is for informational purposes only.

The table below presents the PSD data of the drug substance batches used in the previous QD program as well as the ones planned to be used in the BID program.

D	PSD results for key clinical trial batches QD program			PSD results for key clinical trial batches as planned to be used in the BID program			Proposed Acceptance criteria	
	Phase 2 (S001R1M1)	Phase 3-1 (X005M001)	Phase 3-2 (X006M001)	Z005M002	Z006M003	C001	Commercial	Units
10% 50% 90% 98% span	(b) (4)							

Discussion:

Forest inquired whether FDA had any questions regarding the sponsor's position. FDA stated that they are fine with this.

Question 2a: Characterization of unidentified impurities from the photostability study of the drug substance: Forest believes that no further work is needed to identify the unidentified impurity. Does the FDA agree?

Division Response:

Yes, we agree that no further work is necessary to identify the (b) (4) *impurity.*

Discussion:

No Discussion Required

Question 3a: ***Specification for [redacted] (b) (4) and acceptance criteria for endotoxins: Does the FDA agree with the acceptance criterion of [redacted] (b) (4) EU/g for endotoxins?***

Division Response:

Yes, we agree that you may apply a limit of not more than [redacted] (b) (4) EU/g for the lactose, which is somewhat higher than what is typically recommended (not more than [redacted] (b) (4) EU/g) for lactose to be used in inhalation powder drug products.

Discussion:

No Discussion Required

Question 3b: ***Specification for [redacted] (b) (4) and acceptance criteria for endotoxins: Does the FDA concur that the proposed physico-chemical and microbiological specifications set for the Lactose to be used in future Phase 3 pivotal clinical studies for BID dosing regimen are justified?***

Division Response:

We agree with the test parameters included in the lactose specification. The evaluation of the acceptance criteria will be done as part of the NDA review. We recommend that you provide a letter of authorization in the NDA for a drug master file from the lactose supplier that provides pertinent CMC information for this excipient.

Discussion:

No Discussion Required

Question 4: ***Control Extraction Studies (CES) to be submitted in support of the NDA and the proposed Routine Extraction Tests (RET)***

a. Does the FDA agree that no further Control Extractable Studies are needed?

b. Does the FDA agree that the proposed extractable(s) specifications are acceptable for Phase 3 studies and the NDA filing?

Division Response:

A detailed evaluation of the leachables/extractables studies and the resultant specifications will be done during the review of the NDA. However, we are in agreement with your plan to follow the general approach to addressing the safety of leachables/extractables outlined in the PQRI working group report that you reference.

In addition, your NDA should include details on how you will use qualitative and quantitative extractables profiles, obtained routinely, for indirect control of the composition of the individual components of the device that could impact on the dose delivery performance.

Sponsor Position:

The information presented below is for informational purposes only.

Details on qualitative and quantitative extractables profile to be obtained in routine production will be included as requested in the NDA. In summary, Forest plans to test at least the first 6 inhaler batches to be commercially used and thereafter, one batch per year.

Discussion:

FDA stated that they do not have any comments.

Question 5a: Qualification of the biological reactivity of device parts as per USP <87> and <88>: We do not see a need to perform the biological reactivity tests on any other part. Does the FDA agree?

Division Response:

Yes, we agree that biological reactivity testing need only be performed on the device mouthpiece.

Discussion:

No Discussion Required

Question 6a: DPI devices to be used for different Phase 3 studies and the to-be marketed device for twice daily dosing regimen: Therefore, the FDA's recommendation to use the final Almirall DPI in phase 3 clinical trials is seen as fulfilled and comparative in vitro performance analysis between phase 3 and market supply is no longer needed. Does the FDA agree?

Division Response:

Yes, we agree from the CMC perspective. However, the in vitro performance data (dose delivery and aerodynamic particle size distribution) will be evaluated to assure that the first 30 doses would not be considered to be different from the last 30 doses, as it would appear that patients in the first phase 3 BID trial will not be using the drug product as intended for marketing (i.e., using all 60 doses).

Sponsor Position:

Forest will submit, in the NDA, comparative in vitro performance data (EDU and ACI) between the 30 dose device as used in the first phase III study and the 60 dose device as used from the second phase III study onward. This comparison will include:

- **2 batches of 30 dose device (b) (4) 400 µg strength). EDU through container life on 10 devices. ACI testing beginning and end of container life**

- **2 batches of 60 dose device (b) (4) 400 µg strength)**

  EDU through container life on 10 devices. ACI testing beginning and end of container life

  EDU through the first 30 doses and the second 30 doses on 10 devices. ACI testing beginning, middle and end of container life

Discussion:

FDA stated that what Forest proposed is acceptable.

You propose to use the 30-dose lock out device in one phase 3 BID study and the 60-dose lock out device in the second study. This approach could be problematic if the number of study subjects who use the device throughout the life of the device (60 doses) is insufficient. Provide the number of subjects both in the second phase 3 BID study as well as the long-term safety study that will be using the 60-dose lock out device. If the number of patients using the 60-dose device throughout the life of the device is insufficient, additional patient use data may be required.

Sponsor Position:

The 30 dose and 60 dose devices are manufactured using the final formulation in Forest Laboratories Ireland, the manufacturing site for commercial product using the molds and assembly of devices intended for final commercial product. The only difference between the two devices is the dose counter/indicator ring.

Figures 1 and 2 show the difference between the two rings.

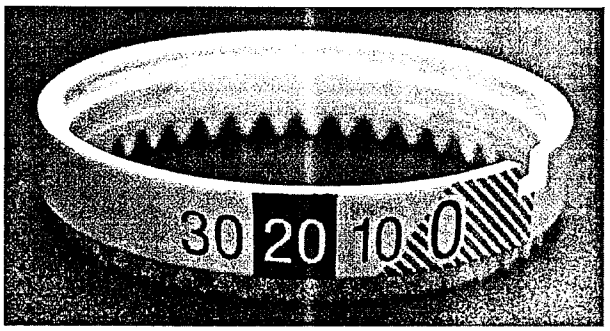


Figure 1 - Counter ring 30

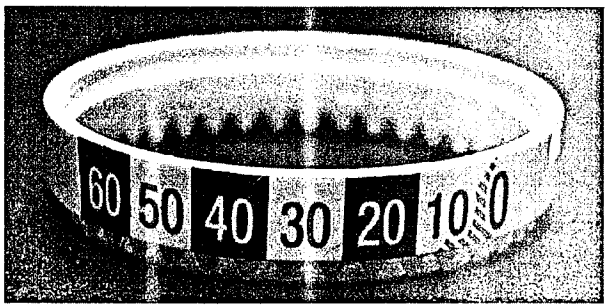


Figure 2 - Counter ring 60

The 30 dose device is intended to be used as physician's sample. Disassembled 30 and 60 dose devices will be sent to the agency for comparison after this meeting.

A total of at least 1060 patients will be using the 60 dose device in the two studies. This translates to a total of at least 7000 devices that will be used of which at least 3000 are expected to be used

Discussion:

FDA inquired as to how many will have the 60 dose lock out. Forest responded that the plan is to have 3,000 devices to lock out at 60 doses. FDA responded that this is sufficient.

***Question 7a:** No effect of device orientation on stability was seen based on QD Phase 3 data and proposed stability matrix plan for the upcoming Phase 3 registration batches for twice daily dosing regimen: Does the FDA agree with the proposed stability matrix for the Phase 3 registration stability for twice daily dosing regimen?*

Division Response:

It is acceptable if you substitute the storage condition of 30°C/65%RH for the conditions of 25°C/75%RH, if desired, to reduce the number of different stability chambers needed to be maintained.

We recommend that the long term storage at 25°C/60%RH include testing at 3, 6, 9, 12, 18, 24 months etc. for the inverted storage position, as it is likely that your statistical

analysis of any trending parameters would necessarily lead to shortened expiry predictions with the matrix of testing that you propose. In general, the use of matrixing protocols for inhalation powder drug products is discouraged due to the complexity of these drug products, which can often lead to non-linear stability trends.

Sponsor Position:

As recommended by the agency, the stability plan is revised (see table below) and now includes long term storage at 25°C/65%RH to reflect 3, 6, 9, 12, 18, and 24 month testing for the inverted storage position.

Does the FDA agree with the revised stability plan?

Revised Stability Plan

	40± 2°C/75± 5%RH			25± 2°C/60± 5%RH							25± 2°C/75± 5%RH				30± 2°C/65± 5%RH			
200µg - INVERTED	**1M**	**3M**	**6M**	**3M**	**6M**	**9M**	**12M**	**18M**	**24M**	**36M**	**3M**	**6M**	**9M**	**12M**	**3M**	**6M**	**9M**	**12M**
Batch 1 (Almirall)	X	X	X	X	X	X	X*	X	X*	X*	X	X	X	X	O	O	O	O
Batch 2 (FRI)	X	X	X	X	X	X	X*	X	X*	X*	X	X	X	X	O	O	O	O
Batch 3 (FRI)	X	X	X	X	X	X	X*	X	X*	X*	X	X	X	X	O	O	O	O

	40± 2°C/75± 5%RH			25± 2°C/60± 5%RH							25± 2°C/75± 5%RH				30± 2°C/65± 5%RH			
200µg - UPRIGHT	**1M**	**3M**	**6M**	**3M**	**6M**	**9M**	**12M**	**18M**	**24M**	**36M**	**3M**	**6M**	**9M**	**12M**	**3M**	**6M**	**9M**	**12M**
Batch 1 (Almirall)	O	O	X	O	O	O	X	O	X	X	O	O	O	X	O	O	O	O
Batch 2 (FRI)	O	O	X	O	O	O	X	O	X	X	O	O	O	X	O	O	O	O
Batch 3 (FRI)	O	O	X	O	O	O	X	O	X	X	O	O	O	X	O	O	O	O

	40± 2°C/75± 5%RH			25± 2°C/60± 5%RH							25± 2°C/75± 5%RH				30± 2°C/65± 5%RH			
400µg - INVERTED	**1M**	**3M**	**6M**	**3M**	**6M**	**9M**	**12M**	**18M**	**24M**	**36M**	**3M**	**6M**	**9M**	**12M**	**3M**	**6M**	**9M**	**12M**
Batch 1 (Almirall)	X	X	X	X	X	X	X*	X	X*	X*	X	X	X	X	O	O	O	O
Batch 2 (FRI)	X	X	X	X	X	X	X*	X	X*	X*	X	X	X	X	O	O	O	O
Batch 3 (FRI)	X	X	X	X	X	X	X*	X	X*	X*	X	X	X	X	O	O	O	O

	40± 2°C/75± 5%RH			25± 2°C/60± 5%RH							25± 2°C/75± 5%RH				30± 2°C/65± 5%RH			
400µg - UPRIGHT	**1M**	**3M**	**6M**	**3M**	**6M**	**9M**	**12M**	**18M**	**24M**	**36M**	**3M**	**6M**	**9M**	**12M**	**3M**	**6M**	**9M**	**12M**
Batch 1 (Almirall)	O	O	X	O	O	O	X	O	X	X	O	O	O	X	O	O	O	O
Batch 2 (FRI)	O	O	X	O	O	O	X	O	X	X	O	O	O	X	O	O	O	O
Batch 3 (FRI)	O	O	X	O	O	O	X	O	X	X	O	O	O	X	O	O	O	O

Full testing at Initial Interval as per EU/US specs
X = Testing Required as per EU/US specs
O = Testing optional
*indicates microbial testing needed

Discussion:

Forest clarified that there is a typographical error. Their position to the Division response should have stated 25C/60%RH, not 25C/65%RH for the storage condition. Forest also stated will do the stability testing for 200mg and 400mg. Forest asked if the Division found the revised protocol to be acceptable. The Division agreed that the revisions were acceptable.

Question 8a: ***Supportive In-Use stability data from QD Phase III batches and commitment to perform in-use stability under limited stability conditions on one batch from Phase 3 registration batches for each formulation strength for twice daily dosing regimen: Does the FDA agree with Forest's commitment to perform in-use stability under minimal conditions on one batch, for each strength, from BID Phase 3 registration batches based upon the in-use stability data already generated from the QD Phase 3 batch?***

Division Response:

Yes, for the most part, however, we recommend that you include the testing of some samples of the higher strength where the cap is not replaced after each actuation. This additional in-use study should include samples that are near the proposed shelf-life expiry.

Sponsor's Position:

Based on your recommendation, we plan to include for additional in-use testing one batch for each dose strength of BID registration batches pre-stored at 25°C/ 60%. The in-use study will be performed over a period of 12 weeks and the samples will be stored at 30°C/ 65% condition with protective cap on in between the actuations in inverted position.

For some samples of the higher dose strength, the cap will not be replaced after each actuation. Also, some samples that are near the proposed shelf-life expiry will be included accordingly.

	Initial	12 m (at time of submission)
200, inverted, cap closed	**X**	**X**
400, inverted, cap closed	**X**	**X**
400, inverted, open cap	**X**	**X**

In addition, supportive data for the 200 µg QD program with an in-use test performed after 22 months (close to the end of the shelf-life) will be submitted in the NDA.

Is this acceptable to the FDA?

Discussion:

FDA stated that this is acceptable.

Question 9a: (b) (4)

(b) (4)

Division Response:

No, we do not concur. Although it is clear that the aluminum foil overwrap would be completely impenetrable to light, it is not clear that this would be the case for the drug product device. Therefore, photostability testing should still be carried out on the filled devices when they are removed from the overwrap, as per ICH Q1B.

Discussion:

No Discussion Required

***Question 10a:** Determination of acceptable mass balance specification for Particle Size Distribution: Normally, multiple actuations and larger volume of air are used for the Dose Content Uniformity (DCU) and the Particle Size Distribution determinations. However, in this case the determination is based on one actuation and only 2 L air volume. Thus, it would be appropriate to have slightly wider criteria* (b) (4) *Does the FDA agree?*

Division Response:

It is reasonable to expect that attaining mass balance close to the target dose delivery for APSD testing with only one actuation and a total volume of 2 L would be more difficult than if multiple actuations were collected with a larger total volume. Therefore, as long as the limits proposed are reasonably reflective of what is typically achieved, it is acceptable to have slightly wider criteria than what is generally recommended by the Agency. The wider criteria proposed will be evaluated relative to the mass balance data provided.

Discussion:

No Discussion Required

***Question 11a:** Characterization studies performed on the drug product: Does the FDA consider the above approaches adequate and see the need for any additional characterization tests to be performed on devices for twice daily dosing regimen in pivotal phase 3 studies?*

Division Response:

All drug product characterization studies should be performed and the data included in the application for the new 400 mcg/60 count presentation. (b) (4)

(b) (4)

Discussion:

No Discussion Required

Question 12a: Labeling of nominal doses and lock-out of the drug product: Does the FDA agree with this approach for addressing the nominal number of doses and lock-out?

Division Response:

The description in the labeling that addresses the number of doses and the lock-out appears to be reasonable.

Discussion:

No Discussion Required

ADDITIONAL COMMENTS

In addition to the in-use studies, we remind you that we recommend that devices that have been partially used in the clinical trials be returned for testing of the pertinent performance parameters (e.g., dose delivery and APSD). These devices are to be tested in addition to any examination or testing performed on complaint devices returned from the trials.

Sponsor's Position:

Based on the FDA draft guidance, part of the QD phase III clinical trials were designed to allow for partially used devices to be returned to the laboratory for in vitro testing in addition to the complaint devices.

The same principle will be applied for the phase III BID studies with the 60 dose device; all complaints and selected partially used devices will be returned to the testing laboratory and analyzed.

Discussion:

No discussion required

ISSUES REQUIRING FURTHER DISCUSSION

None

ACTION ITEMS

None

ATTACHMENTS AND HANDOUTS

Forest provided a document with their positions on questions that wanted to clarify with the Division on May 12, 2009. These positions have been placed under each corresponding question.

Please contact Eunice Chung, at 301-796-4006 with any questions.

Eunice H. Chung, Pharm.D.
Regulatory Project Manager

Drafted by: Eunice Chung /12MAY2009
Initialed by: Craig Bertha/14MAY2009
Ali Al Hakim/14MAY2009

Finalized by: Eunice Chung/14MAY2009

cc: Sadaf Nabavian

Linked Applications	Sponsor Name	Drug Name / Subject
IND 68653	FOREST LABORATORIES INC	LAS 34273 DRY POWDER INHALER (b) (4) (b) (4)

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

/s/

EUNICE H CHUNG
05/14/2009

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type:	Type B Meeting
Meeting Category:	IND
Meeting Date and Time:	March 3, 2009 at 3:00 P.M.
Meeting Location:	Conference Room 1417
Application Number:	IND 68,653
Product Name:	Aclidinium bromide
Received Briefing Package	February 03, 2009
Sponsor Name:	Forest Lab, Inc.
Meeting Requestor:	Amjad Iqbal, Pharm.D. Assistant Director, Worldwide Regulatory Affairs
Meeting Chair:	Badrul A. Chowdhury, M.D., Ph.D. Division Director
Meeting Recorder:	Sadaf Nabavian, Pharm.D. Regulatory Management Officer

Meeting Attendees:

FDA Attendees

Division of Pulmonary and Allergy Products

Badrul A. Chowdhury, M.D., Ph.D., Division Director
Sally Seymour, M.D., Deputy Director for Safety
Susan Limb, M.D., Clinical Reviewer
Prasad Peri, Ph.D., Pharmaceutical Assessment Leader
Feng Zhou, M.S., Statistical Reviewer
Qian Li, Ph.D., Statistical Team Leader
Sally Choe, Ph.D., Clinical Pharmacology Team Leader
Michelle Jordan, M.S., Senior Regulatory Management Officer
Sadaf Nabavian, Pharm.D., Regulatory Management Officer

Sponsor Attendees

Marco Taglietti, MD, Corporate Vice President of Forest Laboratories, Inc. & President of the Forest Research Institute.
John Castellana, Ph.D., Sr. Vice President, Clinical Operations & Biometrics
June Bray, MBA, RPh,Vice President, Regulatory Affairs
Carol Satler, MD, PhD,Vice President, Pulmonary and Cardiovascular Clinical Development
Scott McDonald, PhD, Sr. Director, Project Management
Hassan Lakkis, PhD, Sr. Director, Biostatistics

Stephan Ortiz, RPh, PhD, Sr. Principal Scientist, Clinical Pharmacology & Drug Dynamics
Amjad Iqbal, Pharm.D., Assistant Director, Regulatory Affairs
Linda Kunka, Manager, Regulatory Affairs
Almirall labs
Philippe Bouissou, MD, Development Director
Gonzalo de Miquel, MD, Global Medical Director
Esther Garcia Gil, MD, Global Clinical Leader
Xavier Llaurado, Director Regulatory Affairs

1.0 BACKGROUND

Forest Labs, submitted a meeting request dated December 17, 2008, for a Type B, IND meeting to obtain Division's feedback regarding the development plan for aclidinium bromide (LAS 34273). A briefing package for this meeting was submitted on February 03, 2009. Upon review of the briefing package, the Division responded to Forest Labs' questions via email on February 27, 2009. The content of that email is printed below. Any discussion that took place at the meeting is captured directly under the relevant original response including any changes in our original position. Forest lab's questions are in ***bold italics***; FDA's response is in *Italics*; discussion is in normal font.

If you have any questions, call Sadaf Nabavian, Regulatory Project Manager, at (301) 796-2777.

2. DISCUSSION

QUESTIONS and RESPONSES

Question 1:

In two placebo-controlled, 1-year studies, Study M/34273/30 (ACCLAIM/COPD I) and Study M/3473/31 (ACCLAIM/COPD II), once daily inhaled aclidinium bromide consistently demonstrated a statistically significant difference versus placebo on the primary end point of trough FEV1 at 12 weeks (p<0.001 in each study) with 61- and 63-ml differences from placebo at that time point in each study, respectively. These differences in trough FEV1 values were sustained over a 1-year period…Forest believes (b) (4) (b) (4)

FDA Response:

(b) (4) *Although both pivotal studies demonstrated statistically significant results for the primary endpoint of trough FEV1, a treatment difference of approximately 60 cc is of uncertain clinical significance. You have not adequately evaluated the appropriate dose and dosing interval of aclidinium bromide. We recommend exploration of higher doses and more frequent dosing regimens. Additional dose ranging should include a comparison of the same nominal dose as a once-daily regimen with more frequent dosing regimens. These dose explorations should be completed prior to NDA submission to ensure the selection of the most appropriate and efficacious dose of aclidinium bromide for marketing.*

Discussion

Forest Labs requested clarification on the specific range of treatment difference that will be of clinical significance. The Division responded that there's no set cut-off, but the Division noted that the treatment difference in the Phase 3 studies was significantly lower than the treatment difference observed in the dose ranging program. The Division also noted that the treatment difference for trough FEV1 was significantly less than what was seen with the currently approved anticholinergic medication for COPD. The Division recommended further exploration of the dose level and more frequent dosing to identify the optimal aclidinium dose and dosing interval. This dose ranging should be performed ideally prior to conducting Phase 3 studies. Forest projected (b) (4) (b) (4)

The Division replied that statistically significant results would not be sufficient to justify a BID regimen; the full range of doses and more frequent regimens should be explored. The Division suggested inclusion of the QD dose and more frequent dosing with the same

nominal dose in a formal dose-ranging study as well as active comparator for benchmarking.

The Division asked Forest to clarify what evidence was available to support a BID regimen. Forest referenced earlier dose ranging and the ACCLAIM study data, including peak and trough FEV1values. However, more frequent regimens had not been explored. The Division noted that we are looking for a strong phase 2 program to support the dosing interval. The Division noted that aclidinium may require more frequent dosing like other inhaled anticholinergics. Since Forest already has a sense of what would be the appropriate range for a nominal dose, further dose ranging to evaluate the regimen should not be difficult. An NDA without this type of information to support dose selection would not likely be approved.

Forest labs requested feedback on the level of support that secondary endpoints could provide to bolster the primary endpoint. The Division replied that secondary endpoints were important and should support efficacy. The secondary endpoints in the two pivotal aclidinium trials did not appear robust or impressive based on the information provided in the briefing package. While secondary endpoints may be used to guide dose selection, these data alone were not likely to be sufficient if used in lieu of a formal dose-ranging program.

Forest asked whether a single pivotal study would be sufficient. The Division replied that replication of findings for the to-be marketed dose in at least two different studies would be required. Furthermore, if Forest intends to seek approval for more than one dose level, Forest will need to provide efficacy and safety data that justifies the approval of two different doses. In general, if more than one dose is proposed, justifying the need for two doses will be a high hurdle.

Question 2:

Approximately 1560 patients with COPD have been exposed to 2 or more doses of aclidinium bromide at levels equal to or greater than the 200-mcg dose level intended for clinical use. Out of those patients, 1070 have been exposed for at least 6 months, and 984 have been exposed for at least 1 year. (b) (4)

(b) (4)

FDA Response:

The extent of exposure in the aclidinium development program is consistent with the recommendations of the ICH Guideline for Industry: E1A The Extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life-threatening conditions (March 1995). (b) (4)

(b) (4)

Discussion

No discussion occurred.

Question 3:

Pediatric administration instructions will not be a part of the anticipated label. The pediatric population has not been included in any aclidinium bromide clinical trial to date because COPD is not a disease that affects the pediatric population. Accordingly, Forest plans to request a Full Waiver for pediatric studies. Is the Agency in agreement with this approach?

FDA Response:

While the stated rationale appears reasonable, decisions on pediatric waivers are made at the time of NDA submission.

Discussion

No discussion occurred.

Question 4:

In accordance with FDA Draft Guidance for Industry "Integrated Summaries of Effectiveness and Safety: Location within Common Technical Document," the full Integrated Summary of Safety (ISS) and Integrated Summary of Effectiveness (ISE) will be placed in Module 5 (Section 5.3.5.3). The text portion will be summarized and placed within Module 2 as the Summary of Clinical Efficacy and the Summary of Clinical Safety, Sections 2.7.3 and 2.7.4, respectively. Does the Division agree with the proposed organization and content of the ISS and ISE?

FDA Response:

The proposed organization and content appear acceptable. The application should also include safety analyses based on pooled Phase 3 study data from the two 52-week studies in the ISS.

Discussion

No discussion occurred.

Question 5:

Does the Division agree that the clinical pharmacology package (as listed and described in this Briefing Package) comprises a complete clinical pharmacology package to support the NDA of aclidinium bromide for the treatment of COPD?

FDA Response:

No, we do not agree. We recommend that you include the following clinical pharmacology information at the time of NDA submission:

- *Potential of aclidinium and its major metabolites to induce the major P450 CYP enzymes.*
- *Potential of aclidinium and its major metabolites to act as Pgp substrates.*
- *Effect of hepatic impairment on the pharmacokinetics of aclidinium and its major metabolites.*
- *Effect of covariates (such as race, gender) on the PK of aclidinium and its major metabolites.*

Discussion

Forest labs stated that they will evaluate the major P450 CYP enzyme inducibility and potential for Pgp substrates as the Division recommended. Forest labs, however, stated that chemical hydrolysis rather than esterase mediated hydrolysis seems to be the major route of elimination and that hepatic impairment should not impact the pharmacokinetics of aclidinium and its major metabolites. In support of this, Forest mentioned that they conducted the *in vitro* chemical hydrolysis study where aclidinium was hydrolyzed very rapidly. Therefore, Forest believes that the hepatic impairment study is not needed. The Division responded that the major reason for recommending the hepatic impairment study is because the esterase responsible for aclidinium's hyrolysis has been reported to be produced in the liver and the hepatic impairment, therefore, may affect the esterase mediated hydrolysis of aclidinium. Forest needs to submit their rationale and supporting information why the hepatic impairment study is not needed to the Division for review.

Forest labs stated that in their thorough QT study, they have evaluated pharmacokinetics in 30 men and 30 women and asked whether this was sufficient for gender evaluation. The Division responded that the sample size should typically be adequate enough to be able to detect the difference enough to make dose adjustment if necessary considering the variability associated with the pharmacokinetic of the drug compound. Forest asked that if the variability is not high, whether 30 subjects per gender would be sufficient. The Division replied that preliminarily, the number seems reasonable but the Division still needs to review the study to conclude whether there was sufficient number of subjects. Therefore, Forest should submit the information and make sure that they identify the submission contains the tQT study for gender evaluation.

Forest elaborated further that based on how the compound is hydrolyzed, they do not feel either the race, or [redacted] (b) (4) will impact the pharmacokinetics of the drug significantly and asked for the Division's feedback. The Division stated that will be a review issue.

Question 6:

Dose the Division agree that the nonclinical studies (as listed and described in this briefing package) represent a complete pharmacology, ADME, and toxicology database to support the registration of aclidinium bromide?

FDA Response:

Pending review, the nonclinical studies listed in the briefing package, appear to be adequate to support the registration of aclidinium bromide.

Refer to the ICH guidance for qualification of drug impurities in the drug substance [ICH Q3A(R)] and degradants in the drug product [ICH Q3B(R)]. If applicable, conduct the appropriate toxicity studies to qualify these impurities and degradants. For impurities and degradants that exceed the ICH Qualification Thresholds, conduct a repeat-dose toxicity study in the most appropriate species with a minimum duration of 90 days. For each impurity or degradant with a structural alert for genotoxic potential that exceeds a total intake of 1.5 µg/day, conduct an in vitro mutation assay (i.e. bacterial reverse mutation assay). Levels of the genotoxic impurities and degradants that are structurally similar and expected to interact with DNA in a similar manner should be summed and the total amount should not exceed 1.5µg/day unless they have been toxicologically qualified.

Discussion

No discussion occurred.

Question 7:

Forest intends to submit the raw data in the CDIS-SDTM 3.1.1 format. Is this acceptable to the agency?

FDA Response:

Yes, your proposal is acceptable. In addition, provide the SAS programs used to create the analysis data sets from the SDTM formatted raw data that you are going to submit and SAS programs used to perform the primary and secondary efficacy analyses.

Discussion

No discussion occurred.

Question 8:

Our briefing package provides the Table of Contents for the planned electronic common technical document (eCTD) submission and information on how studies will be organized. Does the Division agree with the organization of the eCTD as outlined?

FDA Response:

The proposed organization and content appear acceptable.

Discussion

No discussion occurred.

Question 9:

In a separate program, Forest plans to further evaluate the safety and efficacy of aclidinium bromide at higher total daily doses to be administered as a BID regimen (e.g. 200 mcg BID and 400 mcg BID)

(b) (4)

b) Forest plans to conduct 2 Phase 3 trials, LAS-MD-35 and LAS-MD-36, to assess the long-term safety of twice daily doses of 200 and 400 mcg aclidinium bromide when administered to subjects with moderate to severe COPD. Combining both LAS-MD-35 and LAS-MD-36 studies, a total of 684 subjects will have been exposed for at least 6 months to either the 200 or 400 mcg BID dose. A total of 131 subjects will have been exposed for 6 months and 105 subjects for 1 year to the 200 mcg BID dose and a total of 343 subjects will have been exposed for 6 months and 105 subjects to the 400 mcg BID dose.

(b) (4)

(b) (4)

FDA Response:

We recommend that you include a placebo group in your safety trials. Without a placebo group, all adverse events will be attributed to aclidinium bromide. We also recommend that you include efficacy assessments periodically, which will help to assess compliance. The adequacy of these patient numbers to support registration of a 200 or 400 mcg BID dosage regimen will depend on the quality of the safety data and the nature of adverse

events and toxicities observed with the drug product. We also recommend that you assess device durability in your clinical program.

Discussion

Forest labs requested clarification on the required safety data. The Division stated that long-term safety data will be needed to support the marketed dose and dosing interval. Forest asked whether the inclusion of a placebo was a requirement. The Division replied that all adverse events will be attributed to the drug in the absence of a placebo, so it was at Forest's risk to conduct a long-term safety study without a placebo arm. The Division noted that similar development programs for other drugs have been able to conduct long-term safety studies with a placebo arm. A placebo controlled study is strongly advised.

Question 10:

A thorough QT (TQT) study, Protocol M/34273/11, was performed with up to an 800 mcg total daily dose of aclidinium bromide; results of which showed no effect on QT prolongation. The final clinical study report for this study was submitted to the Agency on March 14, 2005 (SN 0015). Forest believe that, (b) (4) (b) (4)

FDA Response:

Your TQT study was referred to the QT Interdisciplinary Review Team and is currently under review; specific comments regarding the TQT study may be forthcoming. We recommend serial ECG monitoring and other cardiac safety assessments in your Phase 3 program.

Discussion

No discussion occurred.

Question 11:

The pharmacokinetics of once-daily 400-mcg dosing of aclidinium bromide has been assessed in subjects with chronic renal insufficiency (M/34273/08) and in different age groups (M/34273/09). The pharmacokinetic behavior of aclidinium bromide and its two main inactive metabolites were not altered to a clinically significant extent in subjects with impaired renal function nor was an influence of age observed. Forest believes that the pharmacokinetic behavior of aclidinium bromide observed in these studies would support (b) (4) ***400 mcg BID. Does the Agency agree?***

FDA Response:

Yes, the results of renal impairment study and different age group study conducted at 400 mcg QD dosing can be applied to 400 mcg BID dosing as long as the following requirements are met:

- *The pharmacokinetics of aclidinium bromide and its two main metabolites are linear in the range of therapeutic doses proposed;*
- *There are no safety concerns at the predicted plasma concentrations achieved in patients with renal impairment for both the parent drug and major metabolites at the new proposed dosing regimen.*

Discussion

Refer to our discussion under Response # 5

ADDITIONAL COMMENT

- The genetic locus controlling (b) (4) (b) (4) Please address the impact of (b) (4) on the efficacy and safety of aclidinium bromide.

Discussion

In conclusion, Forest Labs summarized their future plans with the following points:

- Forest does not intend to submit an NDA for the 200 mcg QD dose.
- Forest will have further internal discussion about the need for a formal dose-ranging study and the inclusion of an active comparator in the pivotal studies. If no formal dose-ranging study is conducted, Forest will provide justification for a BID regimen.
- Forest will conduct replicated studies for the to-be-marketed dose.

In response the Division pointed out to Forest labs to consider the following:

- A formal, Phase 2 dose-ranging study prior to the Phase 3 studies was recommended.
- Inclusion of an active comparator in the Phase 3 studies was at Forest's discretion but would be useful for benchmarking the performance of aclidinium.
- If Forest intends to conduct formal dose-ranging, the Division will be open to further discussion about the development program at another End-of-Phase-2 meeting.

In addition, from the CMC's standpoint, it was requested that Forest Labs provide the following in the upcoming CMC meeting briefing package.

- Chemical stability of the drug substance and
- Describe all changes and updates made to the drug-device combination between Phase 2 and 3 and the commercial drug product.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion

4.0 ATTACHMENTS AND HANDOUTS

None provided

Draft: SNabavian/03.11.09

Initialed: PPrasad/03.17.09
SChoe/03.17.09
Slimb/ 03.19.09; 03/20/09
SSeymour/03.19.09; 3/20/09
BAChowdhury/03.20.09

Finalized: SNabavian/03.20.09

Linked Applications	Sponsor Name	Drug Name / Subject
IND 68653	FOREST LABORATORIES INC	LAS 34273 DRY POWDER INHALER (b) (4) (b) (4)

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

/s/

SADAF NABAVIAN
03/20/2009

MEETING MINUTES

MEETING DATE: April 26, 2005
TIME: 9:30 AM - 11:00 AM
LOCATION: Parklawn Chesapeake Conference Room
APPLICATION: IND 68,653
DRUG NAME: LAS 34273 dry powder inhaler (DPI)
TYPE OF MEETING: End of phase 2 (EOP2)
IMTS: 14799

FDA PARTICIPANTS: Division of Pulmonary & Allergy Drug Products, HFD-570

Prasad Peri, Ph.D., CMC Reviewer
Rik Lostritto, Ph.D., CMC Team Leader
Gary Bond, Ph.D., Pharmacologist
Joseph Sun, Ph.D., Supervisory Pharmacologist
Sandra Suarez-Sharp, Ph.D., Clinical Pharmacologist & Biopharmaceutics (CPB) Reviewer
Tetsunari Kihira, Ph.D., CPB Visiting Fellow
Tayo Fadiran, R.Ph., Ph.D., CPB Team Leader
Sally Seymour, M.D., Medical Reviewer
Warner Carr, M.D., Medical Reviewer
Eugene Sullivan, M.D., Deputy Director
Feng Zhou, M.S., Biometrics Reviewer
Sue-Jane Wang, Ph.D., Biometics Team Leader (Actg)
Badrul Chowdhury, M.D., Ph.D., Director
Christine Yu, R.Ph., Regulatory Project Manager

Robert Meyer, M.D., Director, Office of Drug Evaluation II

ALMIRALL PRODESFARMA, S.A.:

Jose Maria Palacios, Executive Director of Research and Development
Antoni Martinez Tobed, Director of Toxicology
Jose Lius Fabregas, Director of Pharmaceutical Development
Antonio Masso, Deputy Director of Pharmaceutical Development
Juan Claramunt, Head Research & Development, Analytical Department
Ferran Pujol, Head of Chemical Development
Paul Crick, Head of CMC Section, Regulatory Affairs
Xavier Luria, Director Clinical Development
Marco Pavesi, Statistician
Gonzalo de Miquel, Senior Medical Advisor
Esther Garcia, Clinical Trial Manager
Ramon Bosser, Head of Project Management and Planning
Davis Roberts, Scientific, Technical and Regulatory Assessor
Xavier Llaurado, Director of Scientific and Regulatory Affairs
Conxi Verdu, Senior Manager, Regulatory Affairs
Stephen Marck Lewington, Director of Global Marketing and Medical Affairs

Consultants:

(b) (4)

BACKGROUND:

Almirall submitted an EOP2 meeting request dated January 5, 2005, to discuss the adequacy of the overall phase 1 and 2 development to support the proposed phase 3 program. They submitted a briefing package dated March 28, 2005, which contained a list of questions to be discussed at this meeting. Upon review of the briefing package, the Division responded to Almirall's questions via fax on April 25, 2005.

Format of Minutes:

Discussions that took place during the meeting are captured directly under the relevant original response, including any changes in our original position. Almirall's questions are in ***bold italics***; FDA's faxed response is in *italics*; discussion is in normal font.

Before the meeting Almirall communicated that they would like further clarification and discussion at the meeting regarding responses to questions 3 (bullet 1), 4 (bullets 2 and 8), 7 (bullets 3, 5, 6), 8, 9, 10 (bullets 1, 3), 11 (bullet 2), 12, 14, 16, 18 (second part), 22b (bullet 1), 26, 29, and 30.

Question 1

The synthesis of micronized LAS 34273 is [redacted] (b) (4) ***To justify selection of these starting materials, and that they have a non-pharmaceutical market, a complete justification according to the new FDA DRAFT GUIDANCE FOR INDUSTRY. Drug Substance Chemistry, Manufacturing, and Controls Information (January 2004) has been prepared. Does the Agency accept the proposed materials as starting materials with a significant non-pharmaceutical market?***

Your approach appears reasonable based on the data presented on pages 2-7 of volume 2 of your briefing package. However, the determination of adequacy is a review issue. We expect complete and appropriate documentation with the submission of the NDA.

Question 2

Does the Agency agree that the proposed physico-chemical and microbiological specifications for the Drug Substance would be adequate to support Phase III clinical trials? It is recognized that this specification will be continuously evaluated as further experience is gained in the manufacturing process and in the clinical trials.

It is adequate to support phase III studies. However, since phase III is considered critical with respect to proposed NDA specifications, your proposed NDA specifications should be equal too or more stringent than those expected for Phase-III and be reflective of your data. Refer to the Draft Guidance for Industry, "Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products," for additional information.

For the NDA, we recommend that you consider the following:

- *A quantitative method for color of the drug substance.*
- *Foreign/particulate matter.*
- *Detailed analyses of the* [redacted] (b) (4)
- [redacted] (b) (4)

(b) (4)

- *Institute separate specifications for micronized drug substance with appropriate attributes.*
- *The proposed PSD acceptance criteria is a review issue.*
- *Provide justification for the deletion of information about organic volatile impurities (OVIs) and bacterial endotoxins from the NDA.*

Question 3

Does the Agency agree that the proposed physico-chemical and microbiological specifications for Lactose Monohydrate would be adequate to support Phase III clinical trials? It is recognized that this specification will be continuously evaluated as further experience is gained in the manufacturing process and in the clinical trials.

Your approach appears reasonable; however, the determination of adequacy for the NDA will be a review issue.

For the NDA we recommend consideration of the following additional parameters:

- *A test for odor, pH, specific rotation, and OVIs.*

  The Division stated that Almirall needs to submit justification why OVI's may not need to be addressed or provide appropriate certification(s).

  Almirall responded that they already have certification regarding these parameters.

  The Division added that if the drug product (formulation/device) does not have any odor, that information should also be included in the specifications.
- *Improve the* (b) (4)
- *Tighten the acceptance criterion for PSD.*
- *For the NDA,* (b) (4) *the acceptance criterion for bacterial endotoxins to NMT* (b) (4)
- *For additional details refer to the draft MDI/DPI Guidance.*
- (b) (4)

Question 4

Does the Agency agree that the proposed physico-chemical and microbiological specifications for the Drug Product would be adequate to support Phase III clinical trials? It is recognized that this specification will be continuously evaluated as further experience is gained in the manufacturing process and in the clinical trials.

- *Your proposed specifications would be adequate to support Phase III clinical trials.*
- *Although acceptability will be a review issue,* (b) (4) *the DDU acceptance criteria to a range of* (b) (4) *as development proceeds.*

  The Division clarified that (b) (4) refers to the mean value of the delivered dose uniformity (DDU) acceptance criteria.
- *Provide individual* (b) (4) *stage data.*
- *Stage groupings as proposed will be a review issue.*

- (b) (4) *mass balance acceptance criteria to* (b) (4)
- *Justification for the use/non-use of secondary packaging for the drug product should be provided.*
- *Label should state the total mass of the formulation contained in the device.*
- *Revise the drug product specifications to clearly state the quantity of formulation per device. The proposed mass per device as stated in the specifications will theoretically provide* (b) (4) *This contradicts with the proposed* (b) (4) *per device.*

  Almirall clarified that (b) (4) They stated that they will update the specifications to the phase 3 device. (See end of minutes for further discussion on the device and lock-out mechanism.)
- *Conduct a ruggedness study to establish the performance characteristics of the drug product (DDU and APSD) during the expected shelf life, and after specific handling (e.g., shipping) and misuse scenarios (e.g., dropping, shaking).*

Question 5

Does the Agency agree with the proposed dosage schemes for Aerodynamic Assessment of Fine Particles and for Dose Content Uniformity, taking into account that 30 doses is the target number of doses?

Your approach appears reasonable; however, the determination of adequacy is a review issue.

Question 6

The nominal number of doses able to be delivered by the inhaler (b) (4) ***The design of the locking mechanism guarantees a minimum of*** (b) (4) ***However this mechanism allows some tolerance with respect to the maximum number of deliverable doses, which in no case will exceed*** (b) (4) ***Is this approach acceptable by the Agency?***

Appropriate in-use data and labeling information will be needed to assess the feasibility and adequacy of this approach

Question 7

The in-use stability study is planned to be carried out with three Phase III batches at release and repeated with samples aged at (b) (4) ***after 6, 12, 18 and 24 months. Does the Agency agree with the proposed in-use stability study?***

- *Your approach appears reasonable; however, the determination of adequacy is a review issue.*
- *Our draft guidance recommends that stability be studied at least twice for the duration of the in use period (e.g., 60-80 days). (One potential option is 1 dose every two days.)*
- *Test for samples near the end of device life (e.g., 20-30 actuations completed).*

  The Division clarified that Almirall can choose at what point in the device life, as long it is toward the end of device life. It was not the Division's intent to recommend testing all the actuations from 20 to 30.
- *Indicate the scale of the drug product size* (b) (4) *in comparison to the commercial scale.*
- *We recommend the use of 30˚C/65% RH conditions as opposed to* (b) (4)

Almirall noted that they will be conducting long term stability testing at 30°C/65% RH as recommended per ICH Guidance.

The Division encouraged Almirall instead to conduct long term stability studies at 25°C/60% RH conditions and accelerated at 40°C/75% RH. The in-use stability study at 30°C/65% conditions will provide data to support excursions outside of 25°C/60%. If there is no data available, storage statement on labeling will have to include a statement such as, "No excursions permitted outside 25°C/60% RH."

- *Clarify the number of doses delivered per DPI ((b) (4) to the number presented on page 23 ((b) (4) (b) (4) at 5 per week).*

  Almirall noted that consecutive administration of the (b) (4) were interrupted by no dosing during weekends. Only (b) (4) will be administered, but those doses will be spread out over 40 days to simulate a 40 day treatment period. (Only (b) (4) per week will be delivered).

  Conduct the stability study with some DPIs with the cap in place.

  Post Meeting Comment

  Clarify if the drug product will have a secondary over-wrap packaging. If so, routine stability studies will need to be conducted with the over-wrap in place.

Question 8

Does the Agency consider the safety features incorporated in the design of the device are adequate for registration purposes?

Your approach appears reasonable; however, the determination of adequacy is a review issue.

We strongly recommend the following additional safety considerations:

- *Use a different color for the cap to distinguish it from the body of the device.*
- *Tether the cap to the body.*

Almirall asked if this was a requirement. (b) (4)

The Division responded that although it is not required, following the Agency recommendations would prevent unintended post-marketing adverse events, such as patients inhaling before removing a cap that is the same color as the body of the device. Although seemingly implausible, it has happened with other devices. In addition, having the cap tethered to the body of the device would prevent misplacement and loss of the cap. When the cap is not in place, foreign objects may enter the body of the device and pose a risk of aspiration. Regarding the company's intention (b) (4) (b) (4) the Division noted that Almirall may need to investigate any effects on moisture and stability.

Question 9

(b) (4)

(b) (4) *Conduct the phase III studies using the to be marketed device, process, container closure, etc..*

- *At the time of submission, the NDA should be complete including full stability using the to be marketed device and the to be marketed process/site/scale.*

  Almirall noted that [redacted]

  The Division stated that they would need to review the data, but there appeared to be substantial differences [redacted] There are risks to LAS 34273 drug development if the phase 3 clinical studies are not conducted using the to-be marketed device, as recommended. All drug product attributes, including performance should be evaluated.

  Almirall stated that they would like to provide additional data [redacted] to the IND.

  The Division responded that the data would be reviewed for the purpose of understanding [redacted] better, not to provide a decision whether it is or is not acceptable to use [redacted] Any conclusions regarding data bridging the [redacted] is a NDA review issue.

Question 10

The NDA will include primary stability data obtained from three batches manufactured at the current industrial site but at [redacted] of the commercial batch size (accelerated and long term data), and complementary stability data for full-scale batches from the intended commercial manufacturing site (at least six months of accelerated and real storage conditions data, both ICH). Does the Agency concur on this strategy demonstrating adequate stability of the Drug Product?

- *Your proposed strategy is acceptable but not recommended.*

  The Division added that there is a major concern with changing the manufacturing site and that bridging studies will have to be performed.

- *Demonstrate that the products from the two sites are comparable in terms of APSD and DDU and that the performance targets have not changed.*

- *We recommend that you include product from the commercial site in some in-use studies if it is available at the time studies are initiated.*

  The Division also suggested that samples of [redacted] be included in the bridging studies.

- *Provide details of all methods used to compare products from the two sites.*

Question 11- Chronic Toxicity Studies

Based on these results, does the FDA consider that the above chronic toxicity studies support the proposed Phase III clinical trials (up to one year of treatment)?

Your chronic nonclinical studies support the proposed Phase III clinical trials, but the following nonclinical issues need to be addressed prior to Phase III.

1. *Genotoxicity*

   Based on genotoxicity data submitted dated April 12, 2005, in which you reported positive Ames and MLA results, we will be recommending follow-up assay(s) pending completion of amendment review.

2. *Reproductive toxicity*

   (b) (4) *for confirmatory Segment II embryo-fetal study in rabbits are not considered likely to produce maternal effects thereby not allowing assessment of potential embryo-fetal toxicity. On this basis, you should consider oral dosing. Male and female fertility studies (segment I) have not been addressed. Make note of the need to satisfy dosing requirements for paternal effects in order to assess potential effects on fertility.*

   Almirall stated that they would like an opportunity to discuss dosing via the oral route. They will submit additional data and request a meeting or teleconference, as necessary.

Question 12

The efficacy data from the phase II dose ranging trial indicate that maximal bronchodilator efficacy is achieved with once daily LAS 34273 200mcg. No safety issues have been reported with this or with the next higher dose (400mcg). Therefore, once daily 200mcg is selected for further phase III development. Does the FDA agree with this strategy?

Based on the submitted results of the dose ranging study (M/34273/22), the 200mcg dose of LAS 34273 appears appropriate for phase III development. However, consider including a LAS 34273 400mcg treatment arm in one study.

Almirall asked for further discussion about including a 400 mcg treatment arm.

The Division noted some interesting findings in the dose ranging study. For instance, the primary endpoint data suggested that the 200 mcg and 400 mcg treatment groups showed an increased effect size at Day 29, compared to earlier visits. In addition, the 400 mcg treatment group demonstrated increasing effect sizes at each visit, whereas, the 200 mcg group did not consistently demonstrate an increasing effect sizes at each subsequent visit.

Although some variabilities in response to secondary endpoints were observed, Almirall stated that the response to 200 and 400 mcg doses were about the same. (b) (4)

(b) (4)

(b) (4)

Question 13

Does the FDA agree with the proposed sequence of the assessments as proposed in the protocol: first BDI/TDI, second SGRQ, third EuroQoL EQ-5D, fourth Patient's Global Assessment of Efficacy?

The sequence of assessments is your choice. The initial patient reported outcome instruments could influence the later patient reported outcome instruments, thus you should administer the most important assessment first. You have chosen the SGRQ as an important secondary endpoint; therefore, consider administering the SGRQ first.

Question 14

Can FDA comment on Almirall's approach for assessing cardiac safety during the Phase III program?

Include Holter monitoring in a subset of patients to assess cardiac safety during your phase III program.

Almirall proposed that they do a subset of about 20% of the patients in North America (about 160 patients).

The Division suggested that Almirall look at labeling for other COPD drugs approved in the U.S. to get a sense of the number of subjects typically assessed with Holter monitors.

Question 15

Study medication will be dispensed every 8 weeks. Three (b) (4) ***will be included in each visit carton. Patients will be instructed to use one device up to exhaustion and return all devices dispensed at the next dispensing visit. With this strategy the estimated proportion of locked-out devices returned by the patient will be between 46 and 65%, ranging that of devices "in use" (used by the patient but not to exhaustion) between 35 and 54%. All devices will be collected and returned to Almirall for analysis at the end of the study. Does the FDA agree to the proposed balance between locked-out and "in use" devices?***

The proposed balance is acceptable as long as some of the "in use" devices are near the end of life and are collected for in vitro analysis. Collect some devices used in the clinical studies for routine testing of pertinent performance parameters and physical attributes (e.g. delivered dose, APSD) after partial use (e.g., after 10, 15, 20 actuations).

Address device durability, including patient reported device problems and comprehensive in vitro analysis of complaint devices in your phase III program.

You have provided little information regarding the dose counter. In addition to in vitro testing of the dose counter, address the durability of the dose counter in the clinical setting in your phase III program [Guidance for Industry: Integration of Dose-Counting Mechanisms into MDI Drug Products].

Question 16

Would the FDA please comment on the adequacy of the proposed classification of symptoms severity (b) (4)

(b) (4)

(b) (4)

Question 17

Please comment on the adequacy of the proposed scale for the Patient's Global Assessment of Efficacy.

The proposed Patient's Global Assessment of Efficacy is not a validated patient reporting outcomes instrument. The proposed scale is acceptable for an exploratory endpoint; (b) (4)

(b) (4)

Question 18

Almirall intends to perform spirometry on Day 1, at 15 and 30 min and 1, 2 and 3 h post first administration for all patients in one Phase III study. Would the FDA please comment on the definition of onset of action (i.e. time after the first dose of IMP administration to achieve a change from baseline in FEV1 of 100mL)?

Your definition of onset of action is not acceptable. Typically, for the product label, we describe the data, such as time to onset of a 15% increase in FEV1 or the change in FEV1 at a certain time.

(b) (4)

Characterize the effect of LAS 34273 on pulmonary function up to 12 hours at the beginning and end of the study in a subset of subjects in both your phase III studies.

Almirall stated that it would be difficult to conduct 12-hour spirometry assessments at every phase 3 study center. They proposed to perform profiles in a separate 6-week study.

The Division replied that, in addition to a separate 6-week study, they would like to see the profiles performed in at least one of the pivotal phase 3 long term studies. This is important in order to be sure that the profile does not change after more chronic dosing. The Division noted that if Almirall chooses this approach, challenges may arise if the profiles at 6 and 52 weeks differ.

Question 19

(b) (4)

Question 20

Almirall intends to perform more intensive lung pulmonary function assessments during the first treatment week (Days 2, 3, 4, and 8) in 10% of the total population of one Phase III study. Would the FDA please comment on the definition of pharmacodynamic steady state [first day within the first week (either Days 2, 3, 4, or 8) in which at least 85% of the maximum trough FEV1 values is achieved].

The determination of steady state will depend upon a review of the data. Establish the pharmacodynamic steady state of LAS 34273 in both phase III studies.

Question 21

Would the demonstration of a significant percentage of patients achieving the "pharmacodynamic steady state" (as per the definition above) on any day during the first week over placebo allow the inclusion of a claim such as (b) (4) ***in the labeling? If so, would the FDA please indicate the percentage of patients required to support this statement.***

We would consider language in the product label regarding the pharmacodynamic steady state. As stated above, the determination of steady state will depend upon a review of the data. Establish the pharmacodynamic steady state of LAS 34273 in both phase III studies.

Question 22

Does the FDA concur that the clinical program as currently designed (completed studies as well as the future studies proposed in the briefing book) is adequate to support the registration of LAS 34273 DPI for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema?

Your proposed clinical program is a reasonable approach to assess the efficacy and safety of LAS 34273 DPI for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema. Approval of LAS 34273 for this indication will be a review issue.

Question 22b

Apart from the specific issues requested above, does the FDA have any additional comments on the placebo controlled phase III protocols?

- *Consider an active comparator arm with a double dummy design.*

  The Division noted that this is not an approvability issue. However, the inclusion of an active comparator may provide helpful comparative information, and would provide insight into the assay sensitivity of the trial.
- *Specify that females with child bearing potential should use two forms of birth control.*
- *Consider including an arm of LAS 34273 400mcg in one study.*
- *Conduct your phase III studies with the to-be-marketed device.*

Question 23

Please comment on the appropriateness of the co-primary variables (trough FEV1-Weeks 12 or 28 and the SGRQ-Week 52).

The proposed procedure for the two primary endpoints is adequate.

Post-meeting comment from the Agency

You indicated that (b) (4) is one of your key target label claims for LAS 34273. In your proposed procedure, (b) (4) (b) (4)

(b) (4)

Question 24

To avoid as much as possible the impact of a different discontinuation rate between groups, the primary time-points selected for the evaluation of trough FEV1 are Week 12 and Week 28. As secondary variable for confirmatory purposes, the analysis trough FEV1 at week 52 will be also performed. Would the FDA please comment on the appropriateness of this strategy?

The primary time-points for the evaluation of trough FEV1, 12 or 28 weeks, are adequate. The analysis at 52-weeks is fine. But, the result of the 52-week analysis can not be used to make any claim as the primary endpoint.

Question 25

Between-group efficacy comparisons will be only performed at main time-points – week 12, 28, and 52. Would the FDA please comment on the appropriateness of this strategy?

The strategy is acceptable.

Question 26

Based on recent experience with studies of similar design, a minimum of 30% discontinuation rate is expected in the placebo group. A lower discontinuation rate is assumed in the active LAS 34273 arm. Would a higher discontinuation rate in placebo arm effect the validity of the study? In such a case, would the FDA please indicate a maximum discontinuation rate acceptable for efficacy assessment?

What is the basis of the assumption of 30% drop out rate for placebo? Minimize the drop out rate as much as possible. The efficacy assessment depends on the drop rate, pattern, and reasons.

Assess the robustness of the results and evaluate the drop out pattern. The LOCF is not enough in the situation of a high drop out rate, especially if those dropouts occurred in the beginning of the study or because of worsening of COPD.

Almirall asked if the Division had suggestions for a different imputation.

The Division stated that LOCF is just one of the methods that are available for missing data imputation and that Almirall should perform a sensitivity analysis to account for the expected differences in dropout rates and to assess the robustness of the efficacy evaluation.

Question 27

In the statistical section of the Phase III protocols, the significance level for testing treatment-by-center interactions in ANOVA and ANCOVA models is stated at p<= 0.10. Is this approach reasonable to the FDA?

This is a review issue.

Question 28

Apart from the specific issues above, does the FDA have any additional comments on the proposed Statistical Analysis Plan?

1. *The rule of the sequential testing for the primary efficacy endpoints needs to be stated in each study protocol and the statistical analysis plan.*

2. *Unless there is a particular reason to suspect an interaction, a model including only main effects of treatments, in this case, the treatment term and the center term, may reasonably be pre-specified as the primary analysis model. In general, treatment-by-center interaction should be performed as an exploratory analysis and is a review issue if heterogeneity among centers exists.*

Question 29

Almirall is seeking the following indication "LAS34273 (b) (4) is indicated for the long-term, (b) (4) maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema." Does the FDA concur that the design of the Phase III studies supports the intended indication?

The design of the phase III studies is a reasonable approach to assess the efficacy and safety of LAS 34273 DPI for the long-term, (b) (4) maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema. Approval of LAS 34273 for this indication will be a review issue.

Almirall added that page 68 of the briefing package has the list of their target label claims, which includes (b) (4)

The Division stated that they are not likely to agree (b) (4)
(b) (4)

Question 30

(b) (4)

Question 31

The protocol as planned excludes COPD patients with major cardiovascular conditions (MI within last 6 months, arrhythmia requiring treatment within the last 12 months, and hospitalization for NYHA class III and IV CHF within the last 12 months). Would the FDA please indicate what impact this exclusion would have for the labeling, assuming adequate cardiovascular safety results in the Phase III studies?

We understand the rationale for the exclusion of subjects with major cardiovascular conditions. That being said, the exclusion of subjects with major cardiovascular conditions could potentially be incorporated into the product label. Ideally, clinical studies would include subjects with co-morbidities expected in the intended population, such as underlying cardiovascular disease.

Question 32

(b) (4)

Question 33

Almirall proposes to instruct patients to (b) (4) ***Would this be acceptable to the FDA?***

No. (b) (4)

(b) (4)

Question 34

The Phase III program will be composed of two studies of essentially equal design. One will be conducted in Western, Central, and Eastern (CEE-Russia, Ukraine, Romania, Poland) Europe and the second one in North America, South Africa, Australia/New Zealand. A minimum of 60% of the patients in the latter will be recruited in North America. Taking into account that no differences in efficacy or safety would be expected due to ethnic or medical practice differences between Western and CEE, Almirall intends to maximize the recruitment potential in CEE for the first study up to 70-80% of the total patients, in the event that Western Europe experiences recruitment difficulties. Would the FDA comment on this strategy?

Your approach is reasonable. You will need to support your assertions at the time of the NDA submission.

We note that your dose ranging study (M/34273/22) included primarily caucasian males. Include subjects representative of the intended population, including females and non-caucasian racial groups, in your phase III studies. The lack of racial and ethnic subgroup data in the pivotal studies would be a review issue. Keep in mind that 21 CFR 314.50 (d)(5)(v) and 314.50 (d)(5)(vi)(a) require the efficacy and safety data be presented for gender, age, and racial subgroups.

Question 35

The number of moderate to severe COPD patients exposed to any dose of LAS 34273 at NDA submission is expected to be approximately 1800. Out of the total patients, 1204 will be exposed for at least 4 weeks to the therapeutic dose (200mcg) and 1020 for 52 weeks. In addition, smaller studies in healthy volunteers or special populations will account for over 300 subjects. Would the FDA comment on the appropriateness of the size of the total database in support of NDA registration?

The size of the proposed database seems reasonable. Keep in mind that a potential safety signal may require additional studies.

Question 36

In this context, Almirall requests the FDA to please comment whether the mass balance study can be conducted using different conditions than those used in the Phase III trials, such as the use of a different device (b) (4) ***the use of a different particle size distribution of the test material or the use of a different administration route (i.v.).***

A mass balance study after the proposed route of administration and using the proposed device is the most appropriate option. However, due to the limitation above stated, you may use a different device to assess the mass balance of LAS 3473. You may also consider assessing the mass balance of the drug under investigation following intravenous (iv) administration using a dose that is supported by preclinical IV data. Which pharmacology/toxicology studies are needed can be addressed by the pharmacology review team.

Question 37

Please comment on the need for this study taking into account the absence of measurable plasma levels of the parent compound and the two main metabolites following administration of the therapeutic dose. The absolute bioavailability of LAS 34273 will only be established at a dose at least 4-fold higher than the therapeutic dose.

Due to the absence of measurable plasma levels of the parent compound and the two main metabolites following inhalation of a therapeutic dose of LAS 34273, assessing the absolute bioavailability of the compound may not be of relevance. However, if the unchanged drug and major metabolites can be measured in urine at the therapeutic dose, we encourage you to assess the absolute BA following inhalation of LAS 34273 (see response to question 36 for preclinical requirements for IV administration of LAS34273).

Question 38

Please comment on the protocol design of Study M/34273/07 to assess whether patients with severe COPD can generate adequate peak inspiratory flow rates to effectively operate the (b) (4) ***DPI compared to mild COPD patients?***

From the limited information provided, the proposed study design appears reasonable.

Question 39

Study M/34273/08: assessment of pharmacokinetic in subjects with various degrees of chronic renal insufficiency.

Please comment on the requirement to conduct this study given the limited data to be obtained as described above.

Whether or not a study to evaluate the effect of renal impairment on the PK of the drug and metabolites is needed will depend on the results of the mass balance study which will reveal the major route(s) of elimination and the knowledge of the relative potency of the metabolites with respect to parent drug. If the unchanged drug and active (potency/abundance) metabolites are eliminated through the kidney, then a renal impairment study is warranted. Metabolites may be measured due to the enzymatic and chemical instability of the parent drug.

Question 40

Study M/34273/09: assessment of pharmacokinetics of LAS 34273 in moderate to severe COPD patients (young and elderly).

The same observations mentioned for the renal insufficiency study are applicable. Please comment on the requirement to conduct this study given the limited data to be obtained.

As mentioned before, if the unchanged drug and major metabolites can be measured in urine at the therapeutic dose, we encourage you to assess the PK of LAS 34273 in COPD patients.

Question 41

Since the metabolism mediated by the cytochrome P450 is a very minor pathway in comparison to the hydrolysis of the ester bond, which is the major metabolic pathway for LAS 34273, Almirall considers that studies in liver impaired subjects or those assessing potential drug-drug interactions would not be necessary. Would the FDA please comment on this position.

The metabolic pathway of LAS 34273 and its major metabolites is inconclusive. In addition, since the relative potency of major metabolites with respect to parent drug is unclear and the acid metabolite's AUC is about 150-fold higher than the parent drug, the lack of an hepatic impairment study is questionable. If the major metabolites are metabolized by a major P450 pathway and if the potency/abundance of major metabolites overshadows that of the parent compound, then an hepatic impairment study is warranted.

Following are additional Clinical Pharmacology and Biopharmaceutics comments for your drug development program:

- *Assess the potential for the parent drug and the major metabolites to act as an inducer (s) or/and inhibitor(s) of major CYP450 enzymes.*
- *Study the effect of age (elderly) on the PK of parent drug and major metabolites.*
- *If applicable, assess the potential for DDI interactions based on the metabolic pathway of major active (potency/abundance) metabolites.*

Question 42

(b) (4)

At this time, the Division requested further explanation about how the dose-counter/lock out mechanism functioned (related to Question 4, the eighth bullet).

Almirall stated the lockout ensures (b) (4) doses, but has a variability between (b) (4) doses.

The Division asked Almirall to explain such variability in the lockout feature of the device. They also asked if there is a possibility that the patient's technique during use may effect the number of doses available. After dose (b) (4) does the counter read zero, but still continue to give doses? These issues raise clinical safety concerns and pose a problem in how to word the Patients Instructions for Use in labeling.

Almirall circulated a sample of the device. They proposed to submit additional information about the physics of why lock-out cannot be made more precise. Patient technique is not a factor in how many doses are available, but additional data on this issue will be available in the future. Almirall noted that although they commit to (b) (4) available doses in the device, additional doses over (b) (4) are also compliant with specifications.

The Division stated that to claim doses beyond (b) (4) are compliant would require testing beyond the labeled claim and that such claims would be difficult to address in labeling.

Almirall asked whether the phase 3 study protocol can be submitted as a request for Special Protocol Assessment (SPA).

The Guidance for Industry, "Special Protocol Assessment," provides specific information about what protocols can be submitted for SPA. It is Almirall's choice whether or not they request SPA, but it was not necessary. The Division stated that they will try to provide timely review of the protocol upon submission.

The Division noted at this time that the Guidance for Review Staff and Industry, "Good Review Management Principles and Practices (GRMPs) for PDUFA Products," has been issued. Stability updates or other amendments submitted **during** the NDA review cycle may not be reviewed in keeping with recommended timelines. The NDA should contain all necessary data and information to support the proposed indication at the time the application is submitted to the Agency.

Almirall noted the following action items:

- Almirall will submit additional data regarding reproductive toxicity and oral dosing and request a separate meeting to address those issues.
- Almirall will submit additional information to the IND regarding the differences between (b) (4) devices, for informational purposes only.

The meeting was adjourned at this time.

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

/s/

Christine Yu
5/18/05 05:48:33 PM

Memorandum of Telephone Facsimile Correspondence

Date: May 18, 2005

To: Thomas N. Deets, Jr., R.Ph., M.S.
U.S. Agent, Regulatory Consultant

Fax: 215-933-6103

From: Christine Yu, R.Ph.
Regulatory Project Manager

Subject: IND 68,653 LAS 34273 DPI
Minutes of April 26, 2005, EOP2 meeting

Reference is made to the meeting/teleconference held between representatives of your company and this Division on April 26, 2005. Attached is a copy of our final minutes for that meeting/teleconference. These minutes will serve as the official record of the meeting/teleconference. If you have any questions or comments regarding the minutes, please call me at (301) 827-1051.

Thank you.