CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-395

CORRESPONDENCE

Boehringer Ingelheim

Boehringer Ingelheim
Pharmaceuticals, Inc.

Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

January 15, 2004

Attention: Badrul Chowdhury, M.D., Ph.D., Director
Division of Pulmonary and Allergy Drug Products (HFD-570)

Re: Spiriva® HandiHaler®
(tiotropium bromide inhalation powder)
NDA 21-395 / Submission #34

Peter Fernandes, M. Pharm
Telephone (203) 798-5337
Cell phone (203) 512-3146
Telefax (203) 791-6262

E-Mail pfernand@rdg.boehringer-ingelheim.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

Clinical, Toxicology and CMC Commitments

Dear Dr. Chowdhury:

Reference is made to the January 13, 2004 telephone conference call with you and members of your Division and Boehringer Ingelheim (BI) during which we discussed a clinical post-approval commitment and options to qualify selected degradation products.

Provided below are our proposed commitments:

Clinical Commitment:

BI acknowledges that the SPIRIVA NDA does not contain sufficient data to exclude any potential effect of tiotropium on QT prolongation as presently being requested by the FDA for new pharmaceuticals with systemic bioavailability. We therefore commit to conducting post approval, a randomized, double-blind study including both a placebo control and a positive control to evaluate the effect of tiotropium on the QT interval. We shall submit the proposed protocol to the Division in 2Q2004 and reach agreement on its acceptability to fulfill this Phase 4 requirement before initiating this study. We commit to submit the final report of this study by —

Toxicology Commitment:

BI commits to conducting post approval, an additional 13-wk inhalation study in Wistar rats to qualify the degradants — and — according to current ICH guidelines. The test articles will be parent compound (Ba 679 BR) spiked with the individual degradants. The aerosol quality (MMAD of — will be sufficient to provide an estimated

Boehringer Ingelheim

lung dose at least 10 fold higher than that estimated for humans administered daily with 22 µm tiotropium bromide monohydrate. We will provide the FDA with the proposed protocol in 1Q2004 (early March 2004) to reach agreement on adequate exposure parameters and derived exposure safety ratios. We request feedback within 30 days in order to provide sufficient time to finalize the protocol and initiate the aerosol technical trials and the main study by mid-2Q2004. To calculate the appropriate aerosol concentrations we request FDA to provide BI with the dose metrics they used to assess the lung dose in study U03-1175. We commit to submit the final report of this study by

CMC Commitment:

BI will add a specific test for degradant to the QC Testing Specification for the drug product and proposes a shelf-life acceptance criterion of < We commit to submit the revised TS, analytical procedure and validation report by the end of February 2004. Based on available stability data which show that quantifiable levels of this degradant his specific QC test will be performed as part of post-approval stability studies This commitment will be incorporated into a revised Post-Approval Stability Protocol and Stability Commitment which will also be submitted at the end of February.

If you have any questions or comments, please contact me by telephone (203) 798-5337 or by fax (203) 791-6262.

Sincerely,

Fernand

Peter Fernandes, M. Pharm.
Director, Drug Regulatory Affairs

Enclosure: 4 Desk Copies for Mr. Anthony Zeccola

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-395

INFORMATION REQUEST LETTER

Boehringer Ingelheim Pharmaceuticals, Inc.
Director, Drug Regulatory Affairs
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

12/10/03

Attention: Peter Fernandes

Dear Mr. Fernandes,

Please refer to your December 12, 2001 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Spiriva (tiotropium bromide) Inhalation Powder.

We also refer to your submissions dated July 31, August 22, October 24, and November 5, 2003.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests.

1. Tighten the acceptance criteria for [redacted] in the drug product to better reflect the data. (Refer to Comments 14.b. & c. in our letter dated December 20, 2002, and Comments 9.a and b. of our Information Request letter dated November 7, 2003.)

2. Since you plan to [redacted], provide an agreement to monitor any resulting problems with the capsules (e.g., if significant damage to capsules were to occur on piercing) on stability, once this change occurs, and to investigate any problems and discuss them with the Agency. (Refer to Comment 14.d. in our letter dated December 20, 2002, and Comment 10 of our Information Request letter dated November 7, 2003).

3. The following comments pertain to your stability update in your amendment dated November 5, 2003:

   a. Rectify the following discrepancy. The original NDA stated that the drug product batch size was [redacted] powder blend) equal to [redacted] capsules, whereas the amendment dated November 5, 2003, gave the same batch size in terms of powder blend, but equated the batch size to [redacted] capsules.

b. The following comment pertains to your stability data for aerodynamic particle size distribution. Provide the following agreements.

(1) You agree to provide data to the Agency from the ongoing stability study in the [redacted] as soon as they are available after samples are analyzed at each time point.

(2) If these future stability data show that there is a real trend of [redacted] on stability, this issue will be discussed with the Agency as soon as possible, and it will be thoroughly investigated.

4. The following supporting DMFs are deficient and letters have been issued to the DMF holders: DMF [redacted]. (This is an expansion of Comment 19 in our IR letter dated November 7, 2003.)

5. When we have reached agreement on specifications (analytical procedures and acceptance criteria), provide an updated Methods Validation package. The MV package should include the following, in addition to information provided in the original MV package: a tabular listing of all samples and standards to be submitted, and certificates of analysis and material safety data sheets for each sample and standard to be provided.

6. Update all specification sheets, SOPs, master batch records etc., as appropriate, in accordance with the changes proposed in your amendment dated July 31, 2003, and subsequent changes.

The following comments pertain to the labeling of the foil blister and the HandiHaler device.

7. You are reminded of the following labeling comments which were discussed with you at our meeting on November 20, 2003:

a. Modify the immediate container (foil blister) labeling to specify "Spiriva (tiotropium bromide) Inhalation Powder" as the drug name.

b. Add drug names (both proprietary and established names) to the labeling imprinted on the HandiHaler device (refer to Comment 20 of our IR letter dated November 7, 2003).

8. Add the following warnings for the patient prominently to the labeling on the device.

a. "For use only with Spiriva capsules."

b. "Do not store the Spiriva capsule in the HandiHaler."

9. You have asked to be able to market as part of the drug product, HandiHaler devices already manufactured without the drug name. Although any labeling printed before approval is performed at your own risk, as a one-time measure you may place the drug name and the patient warnings (see above comments) onto the device by attaching a printed sticker. This modification is only permitted for Handihalers manufactured prior to the date of this letter.

10. [redacted]

The following comments pertain to the *Description* section of the Package Insert labeling:

11. Indicate that Spiriva consists of the capsule *and* the device (currently the *Description* section states that Spiriva consists of a capsule containing dry powder for use [redacted] the HandiHaler inhalation device.)

12. Provide a statement to the effect that the amount of drug delivered to the lungs will vary depending on patient factors such as inspiratory flow and peak inspiratory flow (PIF) through the device, which may vary from patient to patient, and may vary with the exposure time of the capsule outside the blister pack.

13. The *Description* section contains *in vitro* data for the emitted dose at a flow rate of 39 L/min. Add the total air volume for this test in parentheses.

14. The *Description* section indicates that drug is delivered "at flow rates as low as 20 L/min." To include this statement, provide or reference specific *in vitro* test data for the emitted dose at 20 L/min.

The following comments pertain to the *How Supplied* section of the Package Insert labeling:

15. Modify the statement about the imprinting on the device (second paragraph) in accordance with changes requested above.

16. In Paragraph 3, it should be stated that the foil lidding should only be peeled back as far as the "Stop" line printed on the blister foil, to prevent exposure of more than one capsule.

17. Clarify why the "How Supplied" section does not specify a refill presentation (without the device), whereas labels supplied in the amendment dated January 31, 2003, include a [redacted]. Specify the presentations of drug product to be approved in this NDA .

The following comments pertain to the patient's instruction for use:

18. Include the statement (page 5) that the capsules should not be exposed to extreme temperature. In addition, insert this statement in the " [redacted] section of the Package Insert.

19. The statement " [redacted] implies that the capsule may be stored in the HandiHaler. Correct this statement to delete reference to [redacted]

20. In the instructions on page 2 (Figure B), state that the foil lidding should only be peeled back as far as the "Stop" line printed on the blister foil, to prevent exposure of more than one capsule.

21. In the cleaning instructions on page 5, insert a warning to instruct the patient not to use the device when it is wet.

22. In the instruction on page 4 (figure 6) [redacted] vibration of the capsule can be heard.

The following comments pertain to the *carton labels*:

23. Modify the labeling to state that the drug should be used immediately after the packaging over an individual capsule is opened, or else its effectiveness may be reduced (reproduced from Comment 21 of our IR letter dated November 7, 2003). Add this statement to the carton labeling as well as to the Package Insert and Patient's instructions for use, as you have proposed.

24. Make the following statement more prominent and legible: "Capsules should always be stored in the blister and only removed immediately before use." Add the following statement to this instruction: "Open the blister foil as far as the *STOP* line to remove only one capsule at a time."

25. List all excipients on the labels.

26. Increase the font size of the smaller fonts to improve legibility, where feasible.

27. Clarify the "Spiriva®" trademark, as to whether it applies only to the drug (tiotropium bromide) or to the drug and the device together (tiotropium bromide capsule in the HandiHaler device).

If you have any questions, call Anthony Zeccola, Regulatory Management Officer, at 301-827-1058.

Sincerely,

Craig Bertha, Ph.D.
Acting Chemistry Team Leader, DNDC II for the
Division of Pulmonary and Allergy Drug Products, HFD-570
DNDC II, Office of New Drug Chemistry
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/

Craig Bertha

12/10/03 11:58:36 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-395

INFORMATION REQUEST LETTER

11/7/03

Boehringer Ingelheim Pharmaceuticals, Inc.
Director, Drug Regulatory Affairs
900 Ridgebury Road P.O. Box 368
Ridgefield, CT 06877

Attention: Peter Fernandes

Dear Mr. Fernandes,

Please refer to your July 31, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Spiriva (tiotropium bromide) Inhalation Powder.

We also refer to your submissions dated August 22 and October 24, 2003.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. These comments are cross-referenced in parenthesis to our letter dated December 20, 2002. We request a prompt written response in order to continue our evaluation of your NDA.

1. Propose a specific assay procedure and an appropriate acceptance criterion (as previously requested) for the [redacted] in the synthesis of the drug substance, i.e., for [redacted] Provide data justifying the proposed acceptance criterion. (Comment 2b)

2. Provide drug product stability data to demonstrate the acceptability of the wide range of particle sizes of the [redacted] drug substance permitted by the proposed acceptance criteria. In this study, use batches of [redacted] drug substance near the extremes of the acceptance criteria. (Comments 3h, 3i and 3j)

3. The following comments pertain to the acceptance criteria for particle size distribution (PSD) of [redacted] drug substance. Provide a complete data set with all data obtained to date including batch size, date when tested and date of manufacture as well as batch number and PSD data. In addition, indicate [redacted], dates and conditions. Institute an additional cut-off (smaller than [redacted] in the acceptance criteria for better control of PSD. (Comment 4g)

4. Provide available data to indicate whether manufacturing process, length of [redacted] time and/or PSD of the [redacted] drug substance are related to variability of PSD change in the [redacted] drug during and after the [redacted] period. Institute appropriate controls to limit such change. (Comment 5a)

5. Provide multiple batch data for the PSD of the [redacted] lactose soon after the [redacted] process has been completed (e.g., within 1-2 days), and at several time points thereafter. These data should include, for example, testing at a time point 3 months after [redacted] and a time point later than 3 months after [redacted], to allow evaluation of the proposed [redacted] period. Alternatively, modify the [redacted] to [redacted] to be in accord with the data of Table 8, relative to the *dates of* [redacted] Comment 6)

6. This comment pertains to the *Median* Diameter specification for *Particle Size Distribution* for Lactose Monohydrate, [redacted] Tighten the range based on your data (e.g., to [redacted] m). (Comment 9h)

7. The following comments pertain to the master batch record for drug product manufacturing in your submission dated July 31, 2002. (Comments 11 and 12).

   a. The following comment pertains to the [redacted] process for tiotropium bromide. Submit the "protocol of process" mentioned on pages 507 and 508 of Appendix 2 (master batch record).

   b. The following comment pertains to the [redacted] process of the [redacted] tiotropium bromide. Submit the "Suppl. Control Sheet No. MI-9-01 Checklist for [redacted] mentioned on page 509 of Appendix 2 (master batch record).

   c. The following comment pertains to the [redacted] processes of the lactose monohydrate. Submit the "Suppl Control Sheet(s)" mentioned on pages 564, 565, and 567 of Appendix 4 (master batch record).

   d. The following comments pertains to the filled capsule [redacted] process.

      (1) Provide the "Suppl. Control Sheets" mentioned on page 538 of Appendix 3 (drug product master batch record).

      (2) Indicate in the master batch records and in the detailed process description, whether the [redacted]

e. With the exception of the indicated [redacted] process parameters for filled capsules, clarify whether the environmental conditions specified in the manufacturing process and the time frames indicated in your response to our Comment 12, are the same as those used in manufacture of NDA stability batches of drug product and intended for commercial batches.

f. As indicated previously (e.g., in our meeting on January 31, 2003), provide a batch numbering system for the drug product that is linked to specific batches of the filled capsules as well as the specific batches of the Handihaler, since this combination constitutes the drug product.

8. As previously requested in our letter dated December 20, 2002, modify the acceptance criteria for *Appearance* to include a detailed description of the Handihaler device, which is an integral part of the drug product. (Comment 14a)

9. The following comments pertain to specifications for foreign particulates in the drug product (Comments 14b & c).

a. Provide validation data for the [redacted] method employed.

b. Explain the following discrepancy. [redacted]

10. [redacted] of capsules should be better controlled, since it affects capsule integrity as well as rate of degradation of the drug substance in the formulation. Modify the acceptance criteria to set appropriate limits (based on representative data) fo[redacted] of *individual* capsules. (Comment 14d)

11. The following comments pertain to delivered dose uniformity. Indicate how often second tier testing was utilized across the [redacted] data points. Provide the individual data to allow further evaluation of your proposed acceptance criteria. Separately report the accelerated data. Modify the proposed acceptance criteria so that the mean requirement must be met before second tier testing may be performed. (Comment 14h)

12. As we previously requested, modify the method for *Uniformity of Delivered Dose* to utilize a fixed volume of [redacted] air per determination. This is our standard to allow uniformity in the presentation of emitted dose data in the product labeling. Provide

adequate data from the revised test method to confirm the dose-to-dose reproducibility. (Comment 14i)

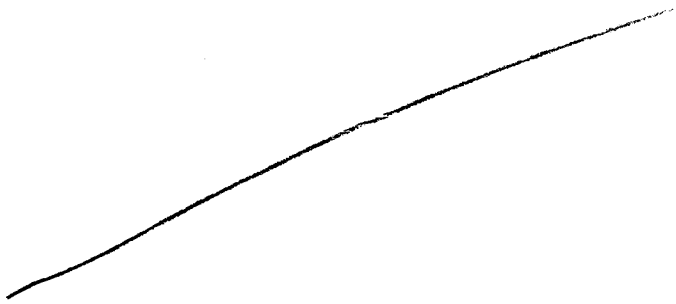
13. Propose controls on mass balance for each aerodynamic particle size distribution analysis. Assess the mass balance relative to the target emitted dose. (Comment 14j(1))

14. Provide assurance that the data used to derive the proposed acceptance criteria for aerodynamic particle size distribution (APSD) of the drug product do not contain any accelerated stability data. Provide a comparison of the data used to support acceptance criteria for APSD with APSD data from batches of drug product used in clinical trials. (Comment 14j(2)-(4))

15. As previously indicated, to limit any potential future changes in the indicated attributes, institute acceptance criteria and a test method(s) to control the solid state physical properties of the drug product formulation (e.g., appearance, size and surface texture). You may list the acceptance criteria as "for information" for a reasonable, defined period of time while you confirm the proposed acceptance criteria. (Comment 14k)

16. The following comments pertain to the container closure system for the drug product (Comment 15b).

    a. The following comments pertain to your commitment for



    b. Rectify the following discrepancy.

c. Justify the reduced target for [redacted] for lidding foil [redacted], in your July 31, 2003, amendment, relative to that for lidding foil [redacted] in the original NDA.

d. Clarify that your numbers for lidding foil, [redacted] and [redacted], refer to the identical materials numbered by your supplier as [redacted] respectively.

e. Indicate if there were any manufacturing changes with the new proposed container closure system, in filling and sealing the blister.

17. The following comments pertain to data and acceptance criteria for the HandiHaler. (Comment 15c)

a. Tighten acceptance criteria for [redacted] (for the mouthpiece, chamber and filter housing) to better reflect your data.

b. Clarify whether HandiHaler batches for the European market (for which release data have been provided) are identical to those proposed for marketing as part of Spiriva in the U.S.

c. Clarify why the specification sheet for the HandiHaler device (Table II.7.3.2:1 (revised)) does not include the specifications for [redacted] which are listed on page 228.

d. Clarify why the acceptance criterion for [redacted] gives the tolerances ([redacted]) but not the target. This also applies to the release data provided for [redacted]

18. Clarify any changes to the NDA except for those indicated in your response to our specific comments. Provide a single, comprehensive list of changes and the rationale for each.

19. The following referenced DMFs are deficient and letters have been issued to the DMF Holders: DMF [redacted] and DMF [redacted] Other DMFs are still being evaluated.

20. The following comment pertains to labels and labeling. Add drug names (both proprietary and established names) to the HandiHaler device, since the drug product is the drug/device combination.

21. Modify the labeling to state that the drug should be used immediately after the packaging over an individual capsule is opened, or *else its effectiveness may be reduced.* Additional labeling comments will be sent following satisfactory resolution of the issues in this letter. (Comment 16a)

22. Explain the tendency for particle size distribution to show a shift to larger particle sizes as flow rates increase in the [redacted] Cascade Impactor test [redacted] data; see page 275). (Comment 17b)

23. Indicate whether your in-use studies of the drug product have shown any individual drug product unit problems with dose build-up, and sudden release to increase emitted dose. (Comment 17c)

24. The following comments pertain to comment 18a of our letter of December 20, 2002.

    a. Revise Table 2 of the stability protocol to include specific analytical method numbers.

    b. Modify the stability protocol to specify sampling plans to be used, to provide assurance that the samples tested are representative of the batch as a whole.

    c. Revise the commitment for the number of batches placed on stability to indicate that it is a function of the number of batches produced in a year, and specify an appropriate function.

25. [redacted]

26. Update your stability data and summaries of those data for drug product in the modified [redacted] packaging configuration, as soon as it is available.

If you have any questions, call Anthony Zeccola, Regulatory Management Officer, at 301-827-1058.

Sincerely,

Craig Bertha, Ph.D.
Acting Chemistry Team Leader, DNDC II for the
Division of Pulmonary and Allergy Drug Products,
HFD-570
DNDC DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Craig Bertha
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-395

8/26/03

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 358
Ridgefield, CT 06877-0368

Attention: Peter Fernandes, M.Pharm.

Dear Mr. Fernandes:

We acknowledge receipt on August 1, 2003 of your July 31, 2003 resubmission to your new drug application for Spiriva (tiotropium bromide) Inhalation Powder.

We consider this a complete, class 2 response to our December 12, 2003 action letter. Therefore, the user fee goal date is February 1, 2004.

If you have any question, call me, at (301) 827-1058.

Sincerely,

{See appended electronic signature page}

Anthony M.Zeccola
Regulatory Management Officer
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Anthony Zeccola
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-395

3/7/02

Boehringer Ingelheim Pharmaceuticals
900 Ridgebury Road
P.O. Box 368
Ridgefiled, CT 06877
Attention: Peter Fernandes

Dear Mr. Fernandes:

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

Name of Drug Product: Spiriva (tiotropium bromide) Inhalation Powder

Review Priority Classification: Standard (S)

Date of Application: December 12, 2001

Date of Receipt: December 13, 2001

Our Reference Number: NDA 21-395

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 13, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be October 13, 2002 and the secondary user fee goal date will be December 13, 2002.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning

this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Drug Products, HFD-570
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at 301-827-1058.

Sincerely,

{See appended electronic signature page}

Anthony M. Zeccola
Regulatory Management Officer
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Anthony Zeccola
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