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Approval Package for:

APPLICATION NUMBER:

21-527

Trade Name: Atrovent HFA

Generic Name: Ipratropium bromide HFA Inhalation Aerosol

Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

Approval Date: November 17, 2004

Indications: Provides for the use of Atrovent HFA (ipratropium bromide HFA) Inhalation Aerosol as a bronchodilator for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease including chronic bronchitis and emphysema.

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APPROVAL LETTER(S)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-527

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P. O. Box 368
Ridgefield, CT 06877-0368

Attention: Jeffrey R. Snyder
Senior Associate Director, Regulatory Affairs

Dear Mr. Snyder:

Please refer to your new drug application (NDA) dated December 6, 2002, received December 9, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Atrovent HFA (ipratropium bromide HFA) Inhalation Aerosol.

We acknowledge receipt of your submissions dated January 13, 24, and 28, February 25, March 3, 12, 13, 21, 24, and 28, April 3, May 7, and 30, June 6, and 12, July 8, October 1, and 2, 2003, and May 14, and 18, June 18, and 25, September 3, October 21, 25, 26, and 29, November 1, 10, 12, and 15, 2004.

The May 14, 2004, submission constituted a complete response to our October 9, 2003, action letter.

This new drug application provides for the use of Atrovent HFA (ipratropium bromide HFA) Inhalation Aerosol as a bronchodilator for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease including chronic bronchitis and emphysema.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the labeling (text for the package insert, and the Patient's Instruction for Use enclosed), and immediate container and carton labels submitted November 12, 2004. Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug. We note that the lot and expiration date will be printed on the bottom flap of the carton.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-527.**" Approval of this submission by FDA is not required before the labeling is used.

We remind you of the following agreements as listed in your letters dated March 5, May 14, October 29, and November 10, 2004, and modified in a telephone conversation with you on November 17, 2004.

1. Conduct a post approval stability study on samples from at least three product batches stored upright and inverted at 40°C/85% RH (to reconfirm the inherent variability of the drug product and to demonstrate that there is not a stability trend). You will test for Aerodynamic Particle Size Distribution (APSD) at the following stability time points in order to fully characterize the stability profile: 0, 1, 2, 3, and 6 months. A complete report of the stability results will be submitted within 12 months of the manufacturing date of the batches. You will inform the Division if there are any remarkable data trends in the interim. As agreed, the type of submission for this data will be discussed with the Division prior to submission.

2. Provide the Division the check weighing rejection rates on the first 10 commercial batches in the Annual report as they become available.

3. Conduct a stability study and provide data as a function of time for foreign particulates and evaluate any trends in the data on three validation/commercial batches of drug product and submit the results of that study post-approval. If manufacture of these batches occurs as planned (b) (4) _____ and will be provided to the Agency. Three drug product cans from each of three validation/commercial batches will be analyzed at each time point. (b) (4) _____ (b) (4) _____ will be used to count, size, and characterize ex-valve foreign particulates (b) (4) _____ and larger. Foreign particulates will be classified into three size ranges for reporting

\geq (b) (4) _____
 \geq _____
 \geq _____

Particle sizing and counting by light obscuration will also be carried out. Based on the results, appropriate acceptance criteria for foreign particulate matter will be set for the drug product.

4. Adopt the following acceptance limits as interim specifications for APSD Stage Groups 3 and 4, for a period of 12 months from the date of approval of our NDA.

Stage Group 3 (stages 5 and 6): (b) (4) (4) _____ (b) (4) _____
 Stage Group 4 (stages 7 and filter): _____ (b) (4) _____

At the end of this 12-month period, you will establish these interim limits as final specifications for Stage Group 3 and 4, unless data are submitted to the Division in a Prior Approval Supplement justifying wider limits for either group. In the event a batch falls outside the interim specification limits during the 12-month period (either at initial release or during stability testing), you may contact the Division to determine the acceptability of the batch for market supply.

5. Provide complete responses within 12 months following approval of the Application to the Agency's comments 7, 8, and 10-15 forwarded to Boehringer Ingelheim in a fax dated Oct. 22, 2004.
6. Conduct an additional 90-day toxicology study in rats that will seek to specifically qualify the leachables in the drug product. You will provide a proposed protocol to the Division for review within 2 months post-approval. You will also discuss and agree on the timing on the outline and the protocol for the 90 day study.
7. List the name of the testing lab that will perform the (b) (4) _____
(b) (4) _____ used in the drug product within twelve months of the approval of the application.
8. Within one month of approval of the application, revise the post approval stability protocol to include a test for (b) (4) _____ in the drug product, to be performed on the first three commercial batches of drug product. The test will be performed "For Information", and no acceptance criteria will be defined. Since this test will be performed only during stability testing as a one-time confirmatory study, the regulatory drug product specifications (located in 3.2.P.5.1) will not include this test. The results above the Limit of Quantitation (LOQ in the testing for (b) (4) (b) (4) _____) will be included in the stability results reported to FDA in the NDA Annual Report. In addition, you will commit to notify the Division in the event that a trend is observed in the levels (b) (4) _____ during the course of the stability study.
9. Make diligent efforts to obtain compositional information from (b) (4) _____
(b) (4) _____, to specify the identity of the individual constituents of these materials. You will request that (b) (4) _____ identify the composition of the materials using standard chemical nomenclature or other terminology that will allow for the determination of chemical structures. We acknowledge that (b) (4) _____ information, and the extent and timing of availability is subject (b) (4) _____. With three months of approval of the application, you agree to provide the Division with any available information.
10. Within 12 months of approval of the application, propose tightened acceptance criteria for the (b) (4) _____ in the drug product specification on the basis of standard process capability analysis (i.e., using the standard criterion of a process capability index, $C_{PK}=1.3$). As noted in the CMC Amendment 014, you may also propose (b) (4) _____ via a prior approval supplement once a sufficient body of data has been accumulated to justify its removal from the specification.
11. Agree that the shelf life will not be extended via the NDA Annual Report. Any shelf life extension will be the subject of a Prior Approval Supplement.
12. Within 12 months of approval of the application, (b) (4) _____
(b) (4) _____

13. Within six months of approval of the application, the specification for the canister (b) (4)-----
(b) (4)-----
(b) (4). The revised acceptance criteria for the specification (b) (4)-----
(b) (4)-----
14. It is our expectation that in accordance with CDER's Guidance to Industry on Dose Counters, Atrovent HFA (ipratropium bromide HFA) Inhalation Aerosol will have a dose-indicating device. Provide a prior approval supplement to incorporate the dose actuation indicator for Atrovent HFA (ipratropium bromide HFA) Inhalation Aerosol within (b) (4)-----

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. We are waiving the pediatric study requirement for this application.

In addition, submit three copies of the introductory promotional materials that you propose to use for Atrovent HFA (ipratropium bromide HFA) Inhalation Aerosol. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Pulmonary and Allergy Drug Products and two copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Ms. Ladan Jafari, Regulatory Project Manager, at (301) 827-1084.

Sincerely,

{See appended electronic signature page}

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

Enclosure : Package insert, Patient Information for Use

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

/s/

Badrul Chowdhury
11/17/04 02:49:33 PM

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DEPARTMENT OF HEALTH & HUMAN SERVICES

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

Attention: Jeff R. Snyder
Associate Director
Drug Regulatory Affairs

Dear Mr. Snyder:

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We acknowledge receipt of your submissions dated December 12, and 16, 2002, January 13, 24 (2), and 28, February 25, March 3, 12, 13, 21, 24, and 28, April 3, and 17, May 7, and 30, June 6, and 12, and July 8, and 25, 2003.

We also acknowledge receipt of your submissions dated October 1 and 2, 2003. These submissions were not reviewed for this action. You may incorporate these submissions by specific reference as part of your response to the deficiencies cited in this letter.

We completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to adequately address the following deficiencies.

1. Resubmit the batch analyses data for all attributes of the drug substance providing actual measured values, where available. If the impurity level was unable to be measured, then the value may be listed as being less than the quantitation limit, otherwise provide data in terms of actual numeric values.
2. Demonstrate that the drug product is a solution at release and stability (e.g., evaluate in — — and provide photographs under various manufacturing and storage condition (e.g., -55°C to 40°C)).
3. Provide a detailed calculation for density estimation of the final formulation.

4. Provide the street addresses for all manufacturing and testing facilities listed in the NDA associated with all responsibilities (including all excipients, components etc.) for the drug product.
5. Provide an estimate of the number of failures of the checkweighing criteria observed for lots 980227 and 980984. Provide an explanation for the lowest value obtained (—) for net fill weight for lot 980227.
6. Provide an estimate of how many samples are typically rejected during the checkweighing during the manufacture of a production batch.
7. Clarify the following statements provided on page 191, vol. 4. of the December 6, 2003 submission.

—

8. Provide validation results that justify that a checkweighing the canisters. —
9. The following comments pertain to —

—

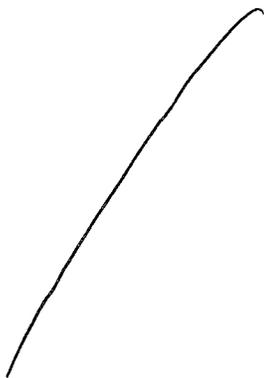
10. The following comments pertain to the excipients used in the drug product.



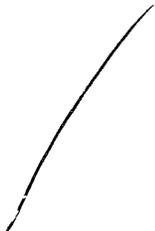
11. The following comments pertain to the specifications of the drug product.
 - a. Revise the description of the acceptance criterion for appearance to state clearly that an _____
 - b. Institute a release acceptance criterion for net content weight of _____ or mean values and individual limit of _____
 - c. Revise the specification for net content weight of the drug product to include mean and individual criteria. Increase the number of cans tested to _____
 - d. Update the citric acid assay specifications to list release and stability acceptance criteria separately. Demonstrate that the proposed lower acceptance criterion (_____ of label claim) for citric acid and its degradants do not negatively impact the stability of the formulation.
 - e. Tighten the acceptance criterion for ethanol assay (e.g., to _____ of labeled claim) based on your data.
 - f. The following comments pertain to impurities in the drug product.
 - (1) Tighten the acceptance criterion for the degradant _____ to _____ based on the stability data.
 - (2) Include an acceptance criterion for total unspecified degradants (greater than the LOQ and less than _____)
 - (3) Tighten the acceptance criterion for the degradant _____ to _____ to reflect the data.
 - g. The following comments pertain to the acceptance criterion for dose content uniformity.

- (1) Based on the average unit dose content obtained for the primary stability and demonstration batches, revise the target medication delivery to 17 microgram/actuation.
 - (2) Delete the phrase _____
- h. The following comments pertain to the measurement and acceptance criteria of Aerodynamic Particle Size Distribution (APSD) of the drug product.
- (1) Express the acceptance criteria for the APSD as measured by the Andersen Cascade Impactor (ACI) as _____
 - (2) Explain the sharp decrease (maximum change _____ in the mass of ipratropium bromide monohydrate collected on _____ within the _____ when stored at 40°C/85% RH. Provide stability data _____ for samples stored at 40°C/85°C _____ to define the profile of the product.
 - (3) Based on the significant changes seen in the profile of the APSD of the fine particle fraction for the drug product, the proposed stage groupings for the measurement of aerodynamic PSD is not justified. _____), resubmit the APSD release and stability data and propose new acceptance criteria _____
 - (4) Revise the acceptance criteria and method to include testing of at least _____ cans per batch for the APSD determination. Include individual and mean acceptance criteria for each stage grouping and provide appropriate data.
- i. The following comments pertain to the acceptance criteria, testing and stability results for valve delivery.
- (1) Explain the following observations noted for the mean valve delivery data for the primary stability batches.
- 

- j. The following comments pertain to acceptance criteria, testing and stability results for extractables and leachables
 - (1) Update Table 2.18:1 (page 126, of volume 8) to list the LOD values for each of the leachables reported.
 - (2) Evaluation of the _____ and further comments on the acceptance criteria for leachables are being withheld pending evaluation of the responses to the Agency's letter dated May 6, 2003.
 - k. Provide release data for spray pattern including representative photographs for the drug product using the proposed method _____. If, possible reduce the number of actuations per analysis for the spray pattern test. Tighten the proposed acceptance criteria so that they are more discriminatory.
12. The following comments pertain to the analytical methods used to characterize, identify and quantify the drug product.
- a. Ensure that each of the chromatographic methods include system suitability tests for tailing and capacity factors with appropriate acceptance criteria.
 - b. Revise the acceptance criterion and the method for appearance of the drug product to clearly state that _____. This pertains to both release and stability.
 - c. The following comments pertain to the identification and _____ assay method by _____
 - e. The following comments pertain to the _____ method _____



f. The following comments pertain to the quantitation of _____



g. The following comments pertain to the determination of medication delivery: _____
_____ method for content uniformity and unit spray content.

(1) Delete the phrase that states that _____

_____ This comment also
applies to other methods where this is stated.

(2) Modify and combine these methods such that _____ canisters are tested at the beginning of the can life and the same _____ canisters are tested for the end of can life.

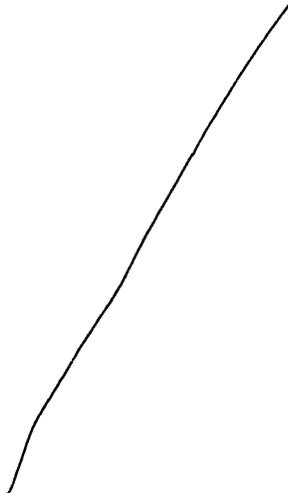
(3) Based on the labeled claim for the drug product _____ (g/actuation) the amount per two actuations would be _____. Hence this would correspond to _____ g/mL when diluted in the diluent. However you have stated (vol. 6, page 192) that the resulting solution nominally contains ipratropium bromide monohydrate a _____ µg/mL. Clarify this discrepancy.

(4) Explain the discrepancy found in the LODs and LOQs for the methods
— there is a — LOD and LOQ for the method
— as compared to —

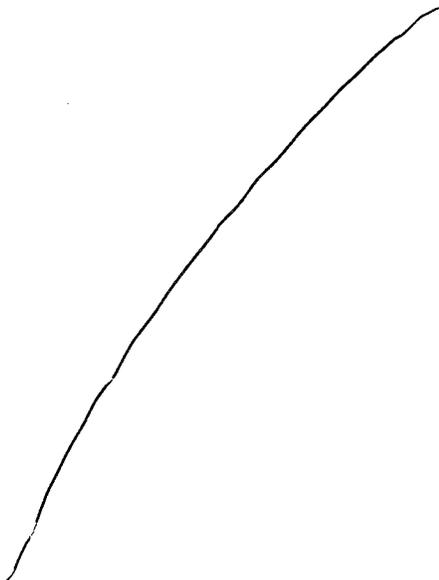
h. The following comments pertain to the determination of APSD (TP-00453-07) for the drug product using the Andersen Cascade Impactor.

- (1) Justify the use of —
- (2) Provide data to demonstrate that —
- (3) Provide details of timelines and procedures used to — Andersen Cascade Impactors.
- (4) Update the method to set a tighter range for acceptance criteria for relative humidity, as appropriate, while performing the APSD analysis.
- (5) Include mass balance testing and evaluation while performing the APSD measurement of the drug product. Since the data suggest greater than — mass balance for the primary stability batches, provide limits to reflect this data.
- (6) Provide the LOD and LOQ for the method in terms of % w/w based on the active.

i. The following comments pertain to the method for quantitation of extractables and leachables — the drug product.



j. The following comments pertain to the — method for — leachables in Atrovent HFA —



13. Provide data for foreign particulates as a function of time, to enable evaluation of any trends in the data over time and of the reliability of the analytical method.
14. The following comments pertain to the studies involved in the characterization of impurities described in the report U02-3347 (vol. 7, pages 199-234).
 - a. Add acceptance criteria for _____ since they appear above the limit of quantitation consistently over time during the stability studies as indicated on page 206, vol. 7.
 - b. As noted in Figure 5.2.1.1: 1, (page 223 of volume 7) the _____ leachables
the _____ methods used for the leachables in the drug product can adequately
quantitate leachables _____ . Demonstrate that
_____ provide the identity of all leachables _____
_____ identified to date.

The following comments pertain to drug product characterization studies.

15. In the experiments demonstrating the stability of the primary unprotected package (vol. 3, page 136), Figure 4:1, clarify if the data generated for APSD by _____ in the formulation is obtained as an average of 20 actuations. Provide the range, mean, and standard deviation of the values obtained for the APSD for these experiments.
16. In the experiments described under the "Effect of Resting Time in vol. 3, page 156" provide the results of the testing on individual actuation basis and not based on a dose (2

actuations). Comments on the conditions needed to re-prime the canister are being withheld until data on the individual actuations are provided.

17. Based on the results of the priming studies modify the patient instructions as follows.

"Patients should "Prime" or actuate the drug product — times prior to taking the first dose from a new inhaler".

18. In the experiments performed under the topic "cleaning instructions" provide data to justify that the weekly cleaning of the actuator is optimal in terms of content uniformity and APSD.

19. In the experiments performed under the topic "Drug Deposition on Mouthpiece and/or Accessories" clarify the number of actuations used to obtain the data provided in Table 9:3 I (vol. 3 page 172). Also, state if the mouthpieces were cleaned during the study and if so when in this study.

20. For studies described under the title "Profiling of Actuators near the Canister Exhaustion" provide the exact conditions / — under which the APSD for the drug product was measured for the experiments.

21. Provide available individual ACI results rather than the pooled data including an evaluation of the APSD and mass balance data from studies — for products manufactured from the second and third generation container closure system.

22. Provide available APSD data comparing the methods / — , for drug product stored at the same time points during stability.

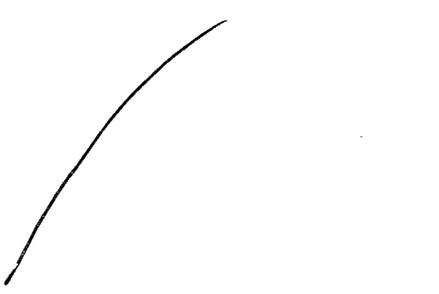
23. The following comments pertain to the studies provided under the heading "Characterization of Particulate Matter in the Formulation."

a. From results in Table 2.2.1:1, you claim that there are no ← found in the drug product. Clarify the statement / —

b. Make appropriate changes to the — methods to more accurately identify and quantitate the —

The following deficiencies pertaining to the container closure system were communicated to you in the May 5, 2003 Discipline Review Letter.

24. For acceptance of each container closure system component, indicate which tests will be performed on receipt of each batch, and which test results will be accepted on the basis of a certificate of analysis (COA). In the latter case, indicate the frequency of your testing to periodically verify the data on the COA, and specify the test site(s).

25. Provide a list of the locations in the NDA for all data provided on certificates of analysis (COA) for container closure components. Ensure that there are representative COA data for each container closure system component. This includes sub-components, e.g., valve components.
26. Drawings with labeled dimensions are only provided for the stem receptacle and spray orifice of the mouthpiece, and legibility of the numbers is poor (vol. 13, pg. 32). Provide legible drawings for the entire mouthpiece component labeled with precise dimensions.
27. Provide the precise dimensional measurements of each valve component.
28. Indicate the manufacturing sites for the valve, mouthpiece and canister.
29. Provide a Letter of Authorization (LOA) to a DMF for information pertaining to the manufacture and controls of the rubber components; alternatively, provide the quantitative composition of the rubber components including all additives, and information pertaining to release controls for the rubber components.
30. Provide specific 21 CFR citations for indirect food additive status, as applicable, for each chemical component of each plastic and rubber material used to manufacture the container closure components.
31. Contact your suppliers to obtain the qualitative chemical composition of the container closure materials. This will facilitate an understanding of potential target extractable and leachable analytes.
32. The following comments pertain to extractables from the 

33. The following comments pertain to extractables from the 



1 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

34. The following comments pertain to leachables in the drug product.

/

35. The following comments pertain to the mouthpiece.

Explain the reasons for all of the changes listed in the Report Revision Statement (vol. 11, page 61) for Report U02-3025, such as changing — Report U023025 describes a — metered dose inhaler mouthpieces.

36. The following comments pertain to characterization and acceptance criteria for the canister.

/

37. The following comments pertain to acceptance specifications for the valve.

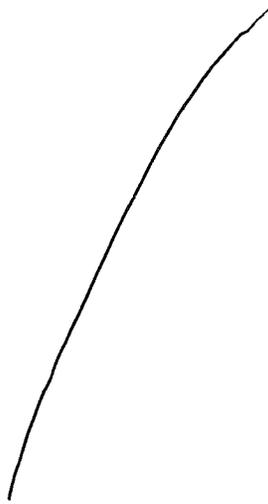
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1 Page(s) Withheld

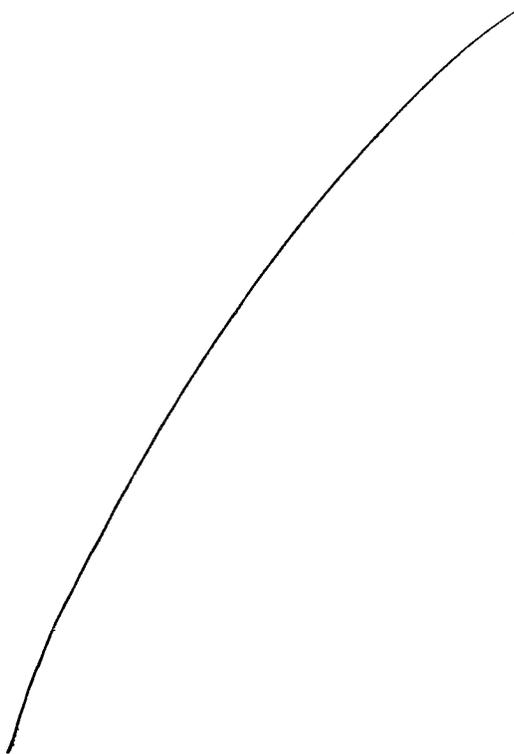
§ 552(b)(4) Trade Secret / Confidential

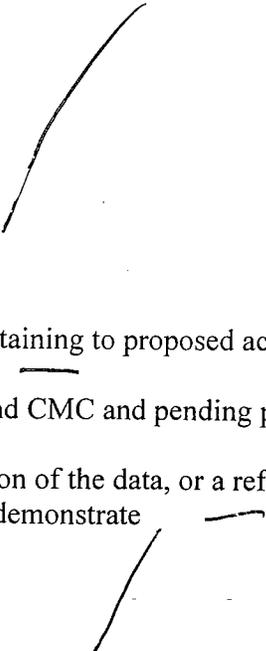
§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling



38. The following comments pertain to acceptance criteria for the actuator/mouthpiece.



- 
39. Additional comments pertaining to proposed acceptance criteria for extractables and leachables. _____ are withheld pending responses to this letter, and CMC and pending pharm/tox evaluation of all relevant data.
 40. Provide data and evaluation of the data, or a reference to where this information may be provided in the NDA, to demonstrate _____
 41. Provide or clarify _____ where the following information may be found: extractable data for _____ which were used to manufacture batches of drug product for leachables testing.
 42. Submit revised draft labeling as shown in the attached marked up labeling. Additional labeling comments may be forwarded upon review of the response to the deficiencies listed above.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). You are advised to contact the Division regarding the extent and format of your safety update prior to responding to this letter.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Sandy Barnes, Chief, Project Management Staff, at (301) 827-1055.

Sincerely,

{See appended electronic signature page}

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

Enclosure