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 drugs. 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

   ≥(b)(4)
   ≥
   ≥

   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) 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) ill 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) t, 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) Within 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) t 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)

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 : Packge 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

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