DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-983

GlaxoSmithKline
Five Moore Drive
Research Triangle Park, North Carolina 27709

Attention: Michael Golden
Product Director, Regulatory Affairs

Dear Mr. Golden:

Please refer to your new drug application (NDA) dated June 30, 1998, received July 1, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ventolin-HFA (albuterol sulfate inhalation aerosol).

We acknowledge receipt of your submissions dated July 10, 23 and 27, September 4, October 6, 12 and 29, November 11, and December 18, 1998, and January 12, February 26, March 31, April 19, May 13 and 19, and June 2, 1999, and June 29, July 6 and 19, September 29, October 12, and December 6 and 22, 2000, and January 4, February 2, 20, and 26, March 30, and April 12 and 19, 2001. Your submission of January 4, 2001, constituted a complete response to our January 3, 2001, action letter.

This new drug application provides for the use of Ventolin HFA for the treatment or prevention of bronchospasm in adults and children 4 years of age and older with reversible obstructive disease and for the prevention of exercise-induced bronchospasm in patients 4 years of age and older.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert and patient package insert submitted December 22, 2000, and carton and immediate container labels submitted February 2, 2001). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved NDA 20-983." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing commitments in your submission dated December 22, 2000, and April 12 and 19, 2001. These commitments are listed below.

1. You have agreed to submit the yield data for the interim heat stress testing of the drug product as agreed to on April 9, 2001, and as discussed during the April 10, 2001, telephone conference, by June 1, 2001. [ ]

2. You have agreed to submit a prior-approval supplement for implementation of the final 100% stress testing of each batch of drug product by the 4th quarter of 2001. A summary of the information to be included in the supplement is provided below.

   [ ]

3. As a follow up to your original commitment to have in place the necessary testing methodology (or through contract laboratories) for the verification of the [ ] test results submitted from [ ] with incoming [ ], we acknowledge your commitment:

   a. To submit an update by May 2001 on the progress and preliminary results of the investigation into the discrepant data obtained by the [ ] testing laboratories for the [ ] and to submit the full report of the investigation and the associated validation information (e.g., methods, results), and comparative data by July 2001.

   b. The May 2001 update will address the following information.

      (1) Explain the apparent discrepancy in the [ ] data provided on p. 4 of the March 30, 2001 amendment in that levels of *N*-nitroso-diethylamine were quantified even though the total nitrosamines are less than the level of quantification [ ]

      (2) Review the nitrosamine acceptance criteria as a larger data base becomes available, and to revise the limits to reflect these data if necessary. Preliminary data in table 3 (p. 4) of the March 30, 2001 amendment suggest that the limits may need to be tightened.

4. We remind you of your commitment to provide, by June 1 2001, to the application and the Agency laboratories, the necessary samples, standards and associated certificates of analysis so that the assessment of your drug substance and drug product methodology can be carried out. Agency laboratories will contact your firm directly with requests for samples. Also submit an updated method with associated validation data by June 1, 2001 or sooner for the determination of the total drug content per can and the apparent concentration of the suspension.

Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol", "Postmarketing Study Correspondence", or "Postmarketing Study Final Report."**

We remind you of the following agreements.

1. Any future proposals for [ ] testing of extractables from incoming [ ] will be submitted as a prior-approval supplement.

2. The future addition of alternate actuator suppliers/manufacturing sites will be supported via a prior-approval supplement.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

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). We note that you have not fulfilled the requirements of 21 CFR 314.55.

We are deferring submission of your remaining pediatric studies for the treatment of asthma in children birth - 2 years of age until February 28, 2004. However, in the interim, please submit your pediatric drug development plans 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.

We are waving the requirements of the pediatric studies for exercise-induced bronchospasm for children up to 3 years of age.

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 notify you within 120 days of receipt of your response whether a waiver is granted. 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.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

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

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Parinda Jani, Project Manager, at (301) 827-1050

Sincerely yours,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research