CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20983

APPROVAL LETTER

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

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

/s/

Robert Meyer
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20983

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-983

Glaxo Wellcome Inc.
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 June 29, July 6 and 19, September 29, October 12, and December 6, 2000, and your correspondence dated August 25, 2000. Your submission of June 29, 2000, constituted a complete response to our July 1, 1999, action letter.

We also refer to your submission dated December 22, 2000. This submission has not been reviewed in the current review cycle. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following. Comment numbers in parentheses refer to those of the October 31, 2000, Agency facsimile.

1. With regard to the interim testing of the drug product using testing methodology with the revised crimp parameters, provide confirmation that the studies correlating external versus internal temperature presented in response to comment 3.b of the August 17, 2000, letter were performed with filled canisters being subjected to the conditions planned for the interim and testing of the product by

2. Include with the mean annualized leak-rate acceptance criterion for the drug product (n = 12 units), the acceptance criterion for the maximum annualized leak-rate for the individual tested valves. The limit should be reflective of typical data with your current crimp parameters and to-be-marketed canister and valve. Submit an update to the drug product specifications reflecting this revision.

3. With regard to your selection of samples for the interim testing procedure, we would like clarification of the following:

   a. Using your proposal, confirm that with a sample size of the chance of having 0, 1, 2, or 3 defective units is no more than % if the true quantity of defective units in any one batch is %;

   b. Provide the protocol from your master batch record that assures random sampling.

4. Revise the individual dose content uniformity acceptance criteria for both tiers by the % of label claim limit to % of label claim to be consistent with the Agency standard. (comment 7)

5. Revise and provide an updated copy to the application of the valve specification acceptance criteria that includes the frequency of periodic testing of individual and mean weight per actuation as previously proposed in the September 29, 2000, amendment, i.e., perform this testing on every 10th batch or once a month, whichever is sooner. (comment 8)

6. The following comments pertain to the stability protocol, expiration dating period and extension, and the in-use period for the drug product (i.e., once the protective packaging is removed by the patient). Revise the stability protocol to reflect each of the following points.

   a. The number of annual stability batches should be commensurate with the production rate and this should be defined in the stability protocol. Revise the protocol to include the commitment for the numbers of annual batches.

   b. The total expiration-dating period includes the maximum of 3 months outside of the protective packaging.

   c. Due to the limited stability data and the dosing variability problems associated with at least one of the primary stability batches, extension of the expiry by the usual route (annual report) is not appropriate. Once a sufficient data base is available to support extension through a statistically-based approach, the removal of this extension limitation can be requested via a prior approval supplement, with inclusion of the supporting data and associated expiration dating analysis.

7. Submit four copies of an updated methods validation package containing the following information: a) composition of the drug product formulation; b) acceptance criteria and methods for the drug substance; c) acceptance criteria and methods for the drug product; d) supporting validation data for the drug substance and drug product methods; e) a list of available samples with their respective sample numbers; f) analytical results for the available samples, i.e., certificates of analysis. Note that the last item may be forwarded with the samples directly to the laboratories upon the request.

8. Submit revised labeling and mockups incorporating the following preliminary labeling comments.

   a. Revise the canister label to include a space for the patient to record the date that the protective packaging was opened. The statement regarding the discarding of the unit after 3 months from this opening date should be clearly associated with this space on the label.

b. The in-use period of 3 months should be indicated on the labels and labeling as in the June 29, 2000, amended versions.

c. The established name of the drug should indicate that the propellant is a hydrofluoroalkane, i.e., albuterol sulfate HFA inhalation aerosol. Revise the labels and labeling appropriately.

d. The following language regarding priming and repriming for the product should be adopted in all appropriate portions of the labels and labeling: "As with all other inhalation aerosol medications, patients should make sure that the canister is seated in the plastic mouthpiece adaptor before each use and the product is primed at specified times. Patients should prime Ventolin HFA Inhalation Aerosol by actuating into the air, away from the eyes and face, 4 times before using for the first time and 4 times when the aerosol has not been used for a period of at least 14 days."

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

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

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. 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.

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 Ms. Parinda Jani, Project Manager, at (301) 827-1064.

Sincerely yours,

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

/s/

Robert Meyer
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 20-983

Food and Drug Administration
Rockville MD 20857

Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, North Carolina 27709

JUL 1 1999

Attention: C. Elaine Jones, Ph.D.
Product Director
Regulatory Affairs

Dear Dr. Jones:

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.

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

(Note: Alphanumerical designations appearing in parentheses following the comments below refer to the comments of the October 26, 1998, Agency letter.)

1. Update and provide a copy of the specification sheet for albuterol base that indicates that the boron level is controlled in the *N*-benzyl albuterol precursor to a concentration of 50 ppm, in response to comment 1.a. of the October 26, 1998, Agency letter.

2. Provide an updated specification sheet for albuterol base that reflects the revisions made in response to comment 1.b. of the October 26, 1998, Agency letter.

3. The cross-validation and particle size data for common batches of drug substance analyzed by the quality control departments indicate that results are shifted lower by % in terms of the median particle size. Furthermore, the determinations of the percentage of particles less than 1 micron differ by up to 18%. (Comments 2.a-d. and 2.g.)

a. Determine the cause for the lack of reproducibility between the analyses from these two sites and take appropriate corrective measures.

b. Revise the specifications for the particle size of the conditioned and micronized albuterol sulfate accordingly once the discrepancies are corrected.

c. Include updated cross-validation data to support the tightened particle size specifications.

4. The acceptance criteria limit of not greater than (NGT) % for the albuterol impurity in the drug substance is not supported by the data provided, which clearly indicate that levels are always less than or equal to % (v1.2, p. 139 of original submission). Reinstate the limit of NGT % for the impurity in the drug substance that was originally in place via the limit for "any other specified" impurity. Provide updated specifications, once agreements on all drug substance acceptance criteria have been finalized. (Comment 3.a.)

5. Update the specification sheet for the drug substance to include acceptance criteria and reference to an identification test that would ensure that the conditioned albuterol sulfate used to prepare the drug product is racemic. Provide a copy of the test method.

6. Update the acceptance specifications for the propellant 1,1,1,2-tetrafluoroethane. You are encouraged to contact your supplier in this regard. (Comment 6.b.)

7. Submit the testing methodology for validation of all propellant supplier's test results reported on certificates of analysis (COA). Also provide representative data from the validating laboratory, identify the validating laboratory, and provide the corresponding COA from the supplier for comparison. (Comment 6.c.)

8. Institute testing to increase the assurance of detection and removal of grossly leaking canisters and those with marginal seal strength or defective valves. Moreover, provide a justification that 2 weeks is an optimal lag time for equilibration and leak detection. (Comment 7.c.)

9. Your conclusion, in the response to comment 8 of the October 26, 1998, Agency letter, that the quality of the drug product is not affected by storage orientation is not supported by data. For example, for the product removed from the protective packaging stored under conditions of 40°C/75%RH for 6 months, canisters stored inverted demonstrated losses of up to % of drug substance on stages 3 – 5 of the , whereas analogous canisters stored upright displayed losses of up to % for this stage grouping. Propose recommendations to be included in the labels and labeling as to the most appropriate storage position(s) for the product. (Comment 8.)

10. The following comments pertain to dosing variability issues for this product and associated testing methodology. [Comments 9.e.(1), 9.e.(2), 9.e.(3), 9.g., 9.i., 9.m.(2) and 12.g.]

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information

37. Provide toxicological data to support the safety of estimated human exposures for the following extractables/leachables from the container closure system.

If published or proprietary toxicological data are not available to estimate safe human inhalation exposure to these chemicals, analyze the chemicals for toxicological structural alerts. Computer programs such as DEREK, TOPKAT, or others, would be appropriate for this purpose. Toxicological data on structurally related compounds may also be submitted to estimate the safety of anticipated human exposure to these extractables.

38. We note that in the two 12-week clinical trials in adolescents and adults (SALA3002 and SALA3005), Ventolin HFA Inhalation Aerosol consistently showed a smaller effect size than Ventolin CFC Inhalation Aerosol, albeit without statistically significant differences between the two formulations. In order to further evaluate the observed difference in effect size, provide any available additional data or analyses to further address this small apparent difference in efficacy and its clinical significance. Such data may include results of additional comparative clinical trials of Ventolin HFA Inhalation Aerosol versus Ventolin CFC Inhalation Aerosol, particularly any studies conducted during periods of asthma exacerbation, such as in a nocturnal asthma model. These numeric differences in efficacy may merit inclusion in the final product labeling.

39. In trial SALA3005 and in foreign post-marketing experience from your [redacted] site, an increased rate of clogging relative to Ventolin CFC Inhalation Aerosol was noted with Ventolin HFA Inhalation Aerosol. To evaluate this difference in actuator clogging, provide additional data or follow-up on factors that might be associated with clogging, such as product age from time of manufacture, use of overwrap, timing of removal of overwrap, the number of doses delivered from the canister, and associated clinical performance as assessed by in-clinic or home-measured pulmonary function assessments. Provide analyses from foreign marketing experience or other post-marketing surveillance to quantify and/or explain the in-use clogging of Ventolin HFA Inhalation Aerosol actuators.

40. In SALA3005, unfavorable changes in physical examinations were observed in the ears, nose and throat category as follows: 8% placebo HFA; 13% albuterol HFA; and 5% albuterol CFC. In light of the increased rate of adverse events of throat irritation seen in the albuterol HFA group, and the greater rate of unfavorable ENT physical examination changes also seen in this group, provide the specific ENT findings from the CRFs that were considered unfavorable relative to baseline for all 3 treatment groups.

41. In addition, it will be necessary for you to submit a revised draft labeling as follows. Line numbers referenced below relate to the labeling version included in your June 30, 1998, submission.

42. You are reminded to address the labeling comments outlined in the Agency letter of October 26, 1998. (Comment 18 and also refer to comment 9 above)

43. Provide the labeling that will appear on the protective overwrap for the drug product. (Comment 18)

The draft package insert and carton and container labels should be modified to reflect the above comments, and the revisions noted in the attached marked-up draft labeling. Further labeling comments will be provided once the aforementioned deficiencies are adequately addressed.

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

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. 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) of the new drug regulations, we strongly encourage you to request an informal meeting with this Division to discuss what further 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, contact Ms. Parinda Jani, Project Manager, at (301) 827-1064.

Sincerely yours,

/S/

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

Enclosure