



NDA 21-254

GlaxoSmithKline
Five Moore Drive
P. O. Box 13398
Research Triangle Park, NC 27709-3398

Attention: Joy Ferrell
Director, Regulatory Affairs

Dear Ms. Ferrell:

Please refer to your new drug application (NDA) dated December 20, 2000, received December 20, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Advair (fluticasone propionate and salmeterol xinafoate) HFA Inhalation Aerosol.

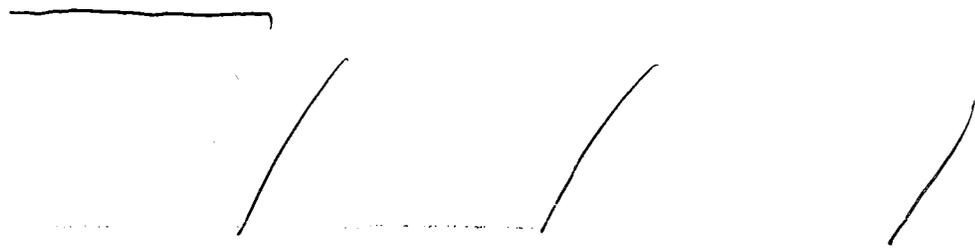
We acknowledge receipt of your submissions dated January 19, 2001, February 9, 14, 22, and 23, March 5, 9, 14, 15, 21, and 30, April 17, and 20, June 5, 12, 28, and 29, September 4, and October 3, 2001.

We also acknowledge receipt of your submission dated October 11, 2001. This submission has not 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:

The following comments pertain to the chemistry, manufacturing and controls (CMC) section of your submission. Most of these comments were conveyed to you in a discipline review letter dated August 13, 2001. When responding, please refer to the comment numbers contained in this action letter.

1. The following comments pertain to control of particle size distribution: 



/ / / /

2. Modify and resubmit the specification sheet for GR106642X propellant (section P2, page 2) to include references to the specific method numbers.
3. Modify all analytical methods to specify _____ as determined by experiments.
4. The following comments pertain to the manufacturing process.

/ / /

e

g.

h. Provide master *packaging* batch records for each strength of drug product.

5. The following comments pertain to the drug product specifications (analytical procedures and acceptance criteria).

a. Select more than one canister per batch per analysis, for all tests in which only one canister is proposed to represent the batch.

b. Update and resubmit all analytical methods to include descriptions of the principles of the analytical procedure used, and lists of all equipment and reagents needed to perform the method. Include changes in accordance with relevant comments in this letter and include method numbers, revision numbers and dates.

c. Provide details of all changes in methods (for all methods, as applicable) used for analysis of critical clinical batches and compare to those used for analysis of NDA stability batches.

d. The following comments refer to ' _____
(Method # _____

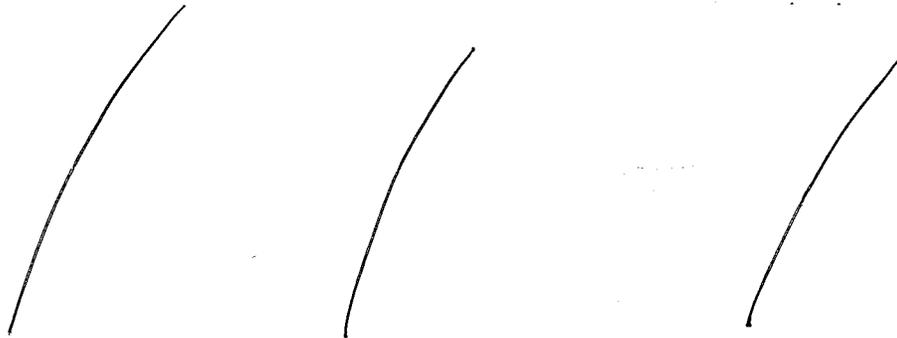
e. The following comments refer to ' _____
(Method # _____

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 Draft Labeling

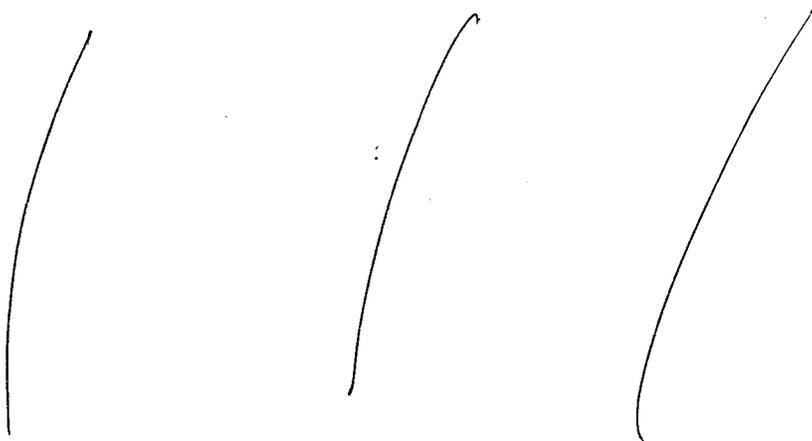
 Deliberative Process

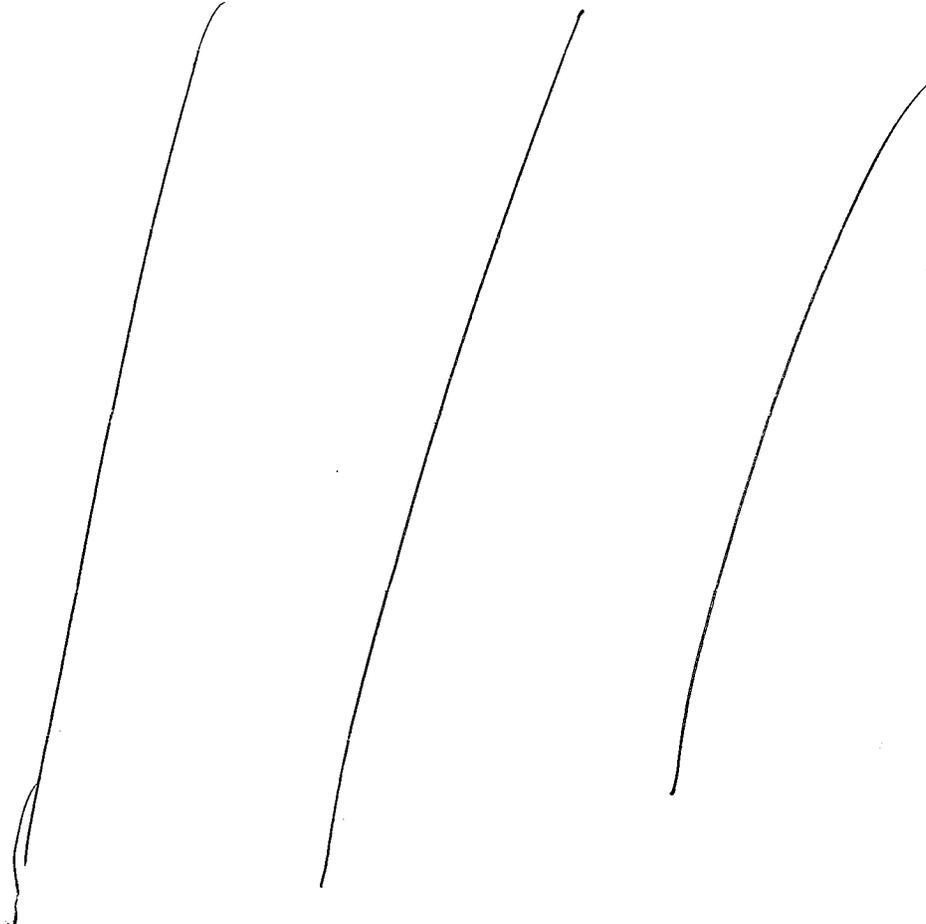


The following comments pertain to the clinical pharmacology and biopharmaceutics portion of your submission.

29. Consider collecting pharmacokinetic data in patients from your future planned Phase 3b-4 study(ies).
30. Explain the reason for the observed differences in salmeterol concentrations in plasma that were documented following the same nominal dose of salmeterol administration (i.e., in study SAS10003) from different dosage strengths.
31. Provide an explanation for the plasma concentrations for fluticasone and salmeterol in study SAS10005 being much higher than those observed in other studies (e.g., SAS10002).

In addition, it will be necessary to submit draft labeling as shown in the enclosed marked up package insert and as listed below. Additional labeling comments will be provided when all the above deficiencies have been 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. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.

- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
 4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
 5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
 6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
 7. Provide English translations of current approved foreign labeling not previously submitted.

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. Ladan Jafari, Regulatory Project Manager, at (301) 827-5584.

Sincerely,

{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

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 Draft Labeling

 Deliberative Process

**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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