# CENTER FOR DRUG EVALUATION AND RESEARCH

**Application Number** 21-077

## APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

NDA 21-077

Food and Drug Administration
Rockville MD 20857

AUG 24 2000

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

Attention: Joy E. Farrell
Director, Regulatory Affairs

Dear Ms. Farrell:

Please refer to your new drug application (NDA) dated March 24, 1999, received March 25, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ADVAIR DISKUS 100/50 (fluticasone propionate 100 mcg and salmeterol xinafoate 50 mcg inhalation powder), ADVAIR DISKUS 250/50 (fluticasone propionate 250 mcg and salmeterol xinafoate 50 mcg inhalation powder) and ADVAIR DISKUS 500/50 (fluticasone propionate 500 mcg and salmeterol xinafoate 50 mcg inhalation powder).

We acknowledge receipt of your submissions dated May 28, June 30, July 16, August 30, September 23 and 29, October 13 and 22, and December 6, 1999, January 13, February 25, March 15, April 18, July 17, 25, and 26, August 14, 18, 22, 23, and 24, 2000. Your submission of February 25, 2000, constituted a complete response to our January 27, 2000, action letter.

This new drug application provides for the use of ADVAIR DISKUS (fluticasone propionate and salmeterol xinafoate) inhalation powder for the long-term, twice-daily, maintenance treatment of asthma in patients 12 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's Instruction for Use leaflet submitted August 24, 2000, and immediate container and carton labels submitted August 23, 2000). 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 21-077." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitment specified in your submission dated August 24, 2000. This commitment, along with completion date agreed upon, is listed below.

> Glaxo Wellcome will provide a summary of the existing pharmacokinetics and pharmacodynamic data on fluticasone propionate in patients with asthma to place in context the apparent gender effects that were observed in the study SFCB3019. In the event the available data are inadequate to determine if a gender effect does or does not exist, Glaxo Wellcome will conduct a clinical pharmacology trial to examine the pharmacokinetics and pharmacodynamic effect of fluticasone propionate administration to male and female asthma patients in an attempt to definitively assess for gender effects. These data will be provided to the Agency by February 2002.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitment, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of the commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

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 fulfilled the requirements of 21 CFR 314.55 (or 601.27) for pediatric patients 12 years of age and above. However, you have not fulfilled the requirements for pediatric patients under 12 years of age. We are deferring submission of the further required pediatric studies until August 2002.

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 request 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 for each strength 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.

APPEARS THIS WAY
ON ORIGINAL

If you have any questions, call Ms. Parinda Jani, Project Manager, at (301) 827-1064.

Sincerely yours.

/S/

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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**Application Number** 21-077

## APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 21-077

.Glaxo Wellcome Inc.
Five Moore Drive
P.O.Box 13358
Research Triangle Park, North Carolina 27709

JAN 27 2000

Attention: Joy E. Farrell
Director
Regulatory Affairs

Dear Ms. Farrell:

Please refer to your new drug application (NDA) dated March 24, 1999, received March 25, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ADVAIR DISKUS — (salmeterol xinafoate 50 mcg/fluticasone propionate 100 mcg inhalation powder), ADVAIR DISKUS — (salmeterol xinafoate 50 mcg/fluticasone propionate 250 mcg inhalation powder) and ADVAIR DISKUS — (salmeterol xinafoate 50 mcg/fluticasone propionate 500 mcg inhalation powder).

We acknowledge receipt of your submissions dated May 28, June 30, July 16, August 30, September 23 and 29, October 13 and 22, and December 6, 1999, and January 13, 2000.

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:

1.

2.

WITHHOLD 3 PAGE (S)

17. The proposed tradenames, "Advair Diskus ——— Advair Diskus ——— and "Advair Diskus ———" are not acceptable, although the prefix Advair is allowable. Select tradenames that clearly reflect that both salmeterol and fluticasone are contained in the product.

18. ——— in the established name is incorrect. Provide appropriate corrections/clarifications, e.g.,

    Established name: (salmeterol 50mcg* and ....)

    Elsewhere on package: "*Each blister contains 72.5 mcg of salmeterol xinafoate, equivalent to 50 mcg of salmeterol base."

19. The following comments pertain to the DESCRIPTION section of the package insert.

    a. Delete the first sentence of the last paragraph relating to the flow rate ———

b. Delete the last sentence in the last paragraph of the DESCRIPTION section and begin this paragraph with [redacted]

c. Provide in vitro dose delivery data modeling the patient flow rate data (see package inserts for other Diskus products.)

20. The disposal instructions in the HOW SUPPLIED section of the package insert will need modification when the in-use periods are agreed upon by the Agency.

21. The following comments pertain to the PATIENT INSTRUCTIONS FOR USE leaflet.

a. The Diskus products are a series of drug products using the same device. To the extent possible, provide consistent labeling for these drug products (e.g., the instructions under How to Use Your ADVAIR DISKUS), by updating the patient package insert of all Diskus products accordingly.

b. Clarify whether the patient inhalation instructions in the proposed labeling (' [redacted] are different from the inhalation instructions used in the clinical trials (e.g., breathe in quickly and deeply – through the Inhaler, not through your nose" was used for Flovent Diskus). Provide patient inhalation instructions for the labeling of all the Diskus products that is consistent and, to the extent possible, fully reflective of the instructions used in the clinical trials.

22. The Patient's Instructions for Use leaflet, carton, overwrap, and Diskus device labeling will need appropriate updating for the trade name, established name, and in-use period when these are agreed upon with the Agency.

23. We note that an expiration date comprised of only numbers is ambiguous (e.g., 03/02). Provide an unambiguous format (e.g., MARCH/2002.)

24. Increase the size and prominence of the discard instructions and include ' [redacted] on the overwrap.

25. Include the following on the Diskus device label.

"Pouch opened _____."

"Use by _____."

26. The CLINICAL TRIALS section should be considerably shortened. Outcomes of Trial [redacted] can be described in reference to outcomes of Trial [redacted] as can secondary endpoints for Trial [redacted]. Verbal descriptions are adequate for onset of action and progression of improvement in these trials. [redacted]. A final determination of the appropriate use of quality of life data in labeling is pending.

27. Per our review and the November 23, 1999, discussion of the Pulmonary Allergy Drugs Advisory Committee, revise the proposed indication for "patients 12 years of age and older [redacted] to better reflect the population studied and better delineate the population expected to benefit from Advair therapy.

28. The labeling (including the box warning) should clarify that these products should not be used for [redacted] indication and that patients who are currently using oral corticosteroids should not be switched directly to Advair.

29. Provide references to the source documentation from the original NDA (volume and page numbers) for the summary data contained in the ADVERSE REACTIONS section.

30. Remove Table – from the DOSAGE AND ADMINISTRATION section.

Further labeling comments will be provided once the aforementioned deficiencies are adequately addressed.

We acknowledge withdrawal of Glaxo Wellcome Australia Ltd., as an analytical testing site for the drug product and your commitment to provide an updated method validation package once the specifications and analytical methods have been agreed upon.

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 combination.

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.

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-40
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 Parinda Jani, Project Manager, at (301) 827-1064.

Sincerely yours,

/S/

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

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Draft labeling