

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 21-254

APPROVABLE LETTER



NDA 21-254

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

Attention: Lorna C. Wilson
Director, Regulatory Affairs

Dear Ms. Wilson:

Please refer to your new drug application (NDA) dated December 20, 2000, received December 20, 2000, submitted pursuant to section 505(b)(2) 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 February 9, 14, 22, and 23, and March 5, 9, 14, 15, 21, 26 and 30, and April 17 and 20, and June 5, 12, 28, 29, and August 13, and September 4 and 18 and October 3, 11, and 30, and November 7, 14, 26, 2001, and April 15, 25, and May 15, and July 31, and August 22, and September 6, and 12, 2002.

The April 15, 2002, submission constituted a complete response to our October 19, 2001, action letter.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, it will be necessary for you to address the following. Related comments previously provided are referenced in parentheses.

1. The following comments pertain to the stability studies of the drug product.
 - a. Investigate and clarify why the primary stability data and the newer _____ stability batch data, _____ each appear in separate clusters for _____ data for dose content uniformity of fluticasone propionate and for salmeterol xinafoate from Advair 220/21 (refer to Figure 97, page 292 of Appendix 11). (Comments 13a-d of our October 19, 2001, letter)
 - b. Clarify the discussion of the results of the statistical analysis of stability data for _____ drug product batches and the _____ controls, so that they better describe _____
_____ Explain what happened in cases _____
_____ Provide a description of the statistical approach used in the analysis of the data. (Comment 1 of our March 25, 2002, letter)

- c. The following comments pertain to Comment 4 of our March 25, 2002, letter.



- d. Provide summary information about individual dose content uniformity in the form of graphical presentations, with separate information for each _____

Indicate on the graphs the limits of _____ This should include primary stability data as well as data from the _____ batches of drug product. (Refer to Section P9.2.3.2 on page 4 of volume 4.1 of your April 25, 2002, amendment.)

- e. There is a general, significant trend throughout all of your stability data, for _____

_____ Provide an explanation, with data, for this difference and provide justification for your proposal _____ (Refer to your April 25, 2002, amendment.)

- f. The following comments pertain to the stability update in your April 25, 2002, amendment.

- (1) The following comment pertains to _____ data. Provide graphical and tabular comparisons of stability data for _____ and control samples.

g. Continue testing for _____ in post-approval stability batches until there is a larger database and all issues _____ are resolved, _____

h. When the acceptance criteria are found to be satisfactory, repeat the statistical analysis of the stability data _____ to re-evaluate the expiration dating period based upon the final acceptance criteria. Comments pertaining to the proposed expiration dating period are withheld at this time, pending resolution of remaining stability and specification issues (including, for example, _____ and analysis of the data by our Division of Biometrics. (Comment 6a of our March 9, 2001, letter and Comment 11f of our October 19, 2001, letter)

i. Provide an update of the _____ stability data.

j. Provide a stability commitment to study the _____ all of the post-approval commitment batches, at all the usual time points (e.g., _____ months for an _____ expiry) and provide a comparison of the stability data between _____ The reason for this is the lack of comprehensive stability data (e.g. across all usual stability time points) for the drug product stored _____ (Comment 6a of March 9, 2001, Information Request Letter)

k. The following comment pertains to the leachable stability study reported in your November 7, 2001, amendment. Continue the comparative study of _____ with analysis at regular time points and quantify individual leachables.

2. Reassess the labeled claim for all strengths of these products, in view of data which appear to show different target values. _____

3.

4.

[Redacted]

5. The following comments pertain to drug substance acceptance criteria:

a.

[Redacted]

b.

6. The following comments pertain to drug product specifications:

a.

[Redacted]

b.

c.

d.

[Redacted]

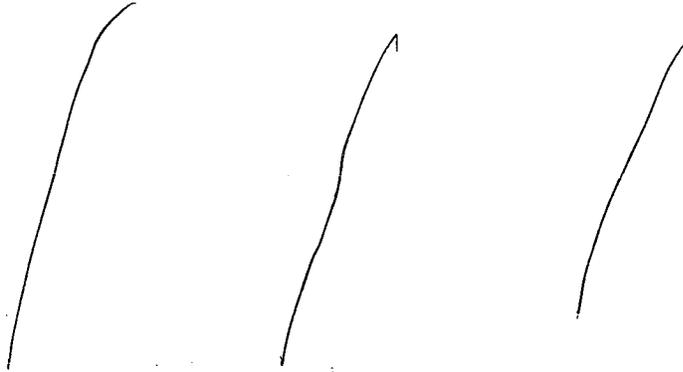
7. The following comments pertain to extractables and leachables from the drug product container closure system.

a. This pertains to _____ NDA 21-254. You are reminded of your commitment, as follows. You committed to “review the suitability of the acceptance criteria as a larger database becomes available, and will revise these limits to reflect these data as necessary. You intend to add to the _____ database until June 2002 and will submit an amendment if the data suggest a tighter specification is appropriate. _____ will also take part in the review and will update their DMF if necessary.” Provide an update of this effort, as the deadline has already passed. (Comment 16 of our October 19, 2001, letter)

b. The following comments pertain to your method for _____ leachables (Method _____, as discussed in your November 14, 2001, amendment.

[Redacted]

- c. The following comments pertain to your specification for _____ extractables in the valve _____ (Comment 6c of our October 19, 2001, letter):



- d. Evaluation of proposed acceptance criteria for individual unnamed extractables from _____ is deferred pending additional information from the holder of DMF _____ (Comment 6d of our October 19, 2001, letter)

- e. This pertains to the acceptance criteria for actuator extractables. Restore the part of the acceptance criterion which specified _____ as originally proposed, to better insure that the composition of the mouthpiece has not changed. _____

- f. Indicate the levels present for the following _____ extractable peaks, relative to the limit of detection (LOD) and limit of quantitation (LOQ) of the analytical method: _____

- g. Develop and implement a specification for drug product leachables and incorporate this into your stability protocols. This is necessary even once it is agreed that an extractable/leachable correlation has been established. In this case, the specification and stability protocol would have a footnote to indicate that a test for leachables is not performed routinely, since extractables are routinely controlled in incoming container and closure system components. This comment is related to previous comments #11c and 17 of our October 19, 2001 letter, and it was discussed in our meeting with you on February 4, 2002. (See also comment 2 of our June 14, 2002, letter)

- h. The following comments pertain to information provided in your response to comment 17 of our October 19, 2001, letter. Additional data are needed to evaluate your proposed correlation between extractable and leachable data. Your response was included in your amendment dated April 15, 2002. (See comment 3 of our June 14, 2002, letter)

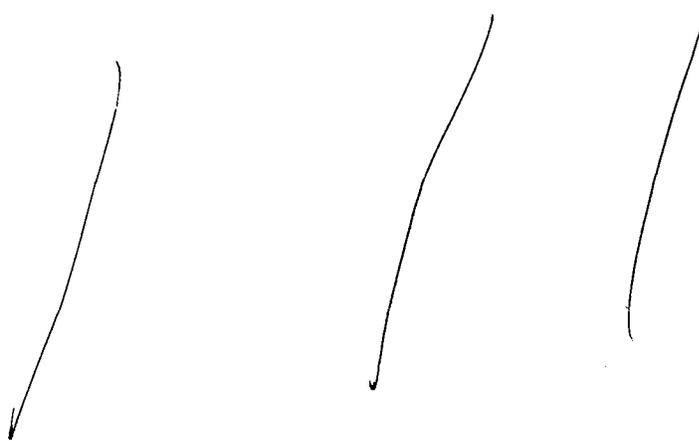
- (1) Provide tabular and graphic summaries of all individual leachable data obtained from all your HFA MDI drug products which use the same or very similar container closure systems. Include all stability time points, and describe stability conditions. In addition, if there were multiple analyses for each leachable from each batch, include means and standard deviations for each batch. Provide means and standard deviations for data for each leachable from each drug product. Include total means and standard deviations for all batches of each leachable, based on individual data obtained from all relevant drug products. Reference in the table the exact locations in the NDA where the methods and their validation reports may be found for each leachable method (you may provide this information in footnotes).
 - (2) Provide tabular and graphic summaries of all individual extractable data obtained for each related container and closure component of your HFA MDIs (except for the mouthpiece/actuator). In addition, include means and standard deviations for each extractable from each component. Component data may be grouped for components with identical chemical compositions from the same supplier, as long as they are clearly identified. Reference in the table the exact locations in the NDA where the methods and their validation reports may be found for each extractable method (you may provide this information in footnotes).
 - (3) Indicate batch numbers of all container closure components for which extractable data are provided, and indicate batch numbers of all components used in drug product or placebo for which leachable data are provided.
 - (4) For the above requested information, indicate the LOD and LOQ of each method used, and provide the extractable data in terms of extrapolation to mcg/inhaler. Also provide a conversion formula to convert mcg/inhaler back to ppm in the component. Insure that the method LOQ and LOD are listed as footnotes to each table in which the data "<LOQ" or "<LOD" appear.
- i. This comment pertains to cases in which specified leachables are greater in amount per can than the values extrapolated from the extractables data for the same batches of container and closure components. Improve the extractable methods to increase the levels of component extractables obtained, such that they are greater than the levels of the corresponding leachables, on a per can basis. (See comment 4 of our June 14, 2002, letter)
 - j. Clarify Tables 164 and 165, page 342-3 of Appendix 11 of your amendment dated April 15, 2002, to indicate the number of lots represented by both the extractable and leachable data, for each component or drug product/placebo analyzed, and include standard deviation values for each extractable and leachable. (See comment 5 of our June 14, 2002, letter)

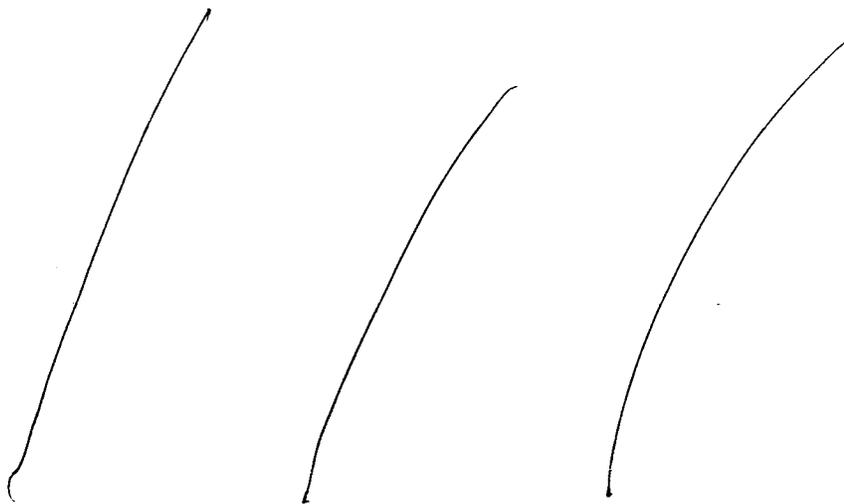
- k. In response to your request in your telephone facsimile of July 19, 2002, we provided the following comments, pertaining to clarification of comment 2 in our June 14, 2002, information request. Our comments were provided in a telephone facsimile sent on August 2, 2002.

We cannot determine the acceptability of your proposed approach to develop leachable specifications until we review the submission. Part of what is required for establishing an extractable/leachable correlation is sufficient data and number of batches at enough time points to determine any trends and to give confidence in the data. In your response, please provide the following additional information:

- (1) Indicate any leachables found which were not detected as component extractables for each HFA drug product.
- (2) Indicate whether the same methods were used for leachable quantitation as for extractable quantitation, and provide the limit of detection (LOD) and limit of quantitation (LOQ) for each method, in a manner that will allow comparison on a "per canister" basis.
- (3) Indicate whether the leachable methods could detect all of the extractables that have been detected in components of the container closure system, if they were present in the drug product, based upon the validation data.
- (4) Leachable specifications should be established for all individual, specified leachables from all sources, as well as for individual unspecified leachables and total leachables.

- l. The following comments pertain to your method _____ for assay of _____
_____ method validation data, and acceptance
criteria (July 31, 2002, amendment) and they pertain to _____





- m. As previously indicated, include leachables in the stability protocol, along with acceptance criteria. We are not yet in agreement that the extractable/leachable correlation has been fully established. Once the Agency is satisfied that there are enough data to demonstrate a reliable extractable/leachable correlation, then the leachables test parameter in the stability protocols may have a footnote indicating that it is not routinely tested, since the extractables are routinely controlled in the components of the container closure system. Review of extractable/leachable issues including the extractable/leachable correlation, component specifications for extractables, drug product specifications for leachables, and a safety assessment of extractables and leachables are deferred pending receipt and review of additional information, requested in our information requests dated June 14 and August 2, 2002. (Comment 11c of our October 19, 2001, letter)

- n. Rule out the presence of _____ extractable/leachable because of potential safety concerns, since the _____ components are _____. Develop a method that can measure _____ in the drug product, e.g., _____ analysis.

- o. Provide copies of chromatograms from recent extractables testing for at least three batches of valve components manufactured from _____.

- p. Provide a commitment to reevaluate plastic valve component extractables and modify the analytical method(s) to enable detection of other components of the plastic _____. _____ The commitment should include an agreement to provide data using the modified method.

8. The following comments pertain to components of the container closure system.
- a. Modify the visual inspection acceptance criteria for assembled valves, including details, for example, _____

_____ (Comment 6a(1) of our October 19, 2001, letter)
 - b. Provide a progress report on the development of the method for valve actuation force, collection of data, and establishment of acceptance criteria. You have indicated that this work would be completed by the end of 2002. (Comment 6a(2) of our October 19, 2001, letter)
 - c. Change or modify the _____ method as necessary to _____
_____ (Comments 8f(1 and 2) of our October 19, 2001, letter)
 - d. Continue investigations directed towards the improvement of drug product performance, by use of _____
_____ (Comment 12b(2) of our October 19, 2001, letter)
 - e. Provide a time line for completion of the _____
_____ for this drug product, and provide a summary of the progress and the current status of these efforts. (Comment 28 of our October 19, 2001, letter)
9. Indicate differences in the _____ process proposed in NDA 21-254 compared to that of the _____ process. There may be additional comments in the future on the subject of the _____ process, depending on your responses to deficiencies in this NDA. Respond here to deficiencies of _____ if they are at all applicable to Advair HFA Inhalation Aerosol. (Comment 4g of our October 19, 2001, letter)
10. Clarify how the additional validation studies for the _____ procedure, performed for the Ventolin HFA product, apply to Advair HFA Inhalation Aerosol, _____
_____ Provide appropriate data. (Comment 26 of our October 19, 2001, letter)
11. As previously requested, address the issue of _____
_____ (Comment 12d of our October 19, 2001, letter)

4 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

We recommend that a meeting be held to discuss and help resolve the above issues, prior to your submitting a response.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). You are advised to contact the Division regarding the extent of your safety update prior to responding to this letter.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Pulmonary & Allergy Drug Products 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, MD 20857

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 (or 601.27). We are deferring submission of your pediatric studies until July 31, 2003.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. 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) 301-827-1084.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Acting Director
Division of Pulmonary & Allergy Drug Products (HFD-570)
Office of Drug Evaluation II
Center for Drug Evaluation & Research

**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
10/16/02 02:30:16 PM