

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

NDA 21-254

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

Patent Information

Item 13 of NDA 21-254
Pursuant to 21 C.F.R. § 314.53
for
ADVAIR™ HFA Inhalation Aerosol

The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name: ADVAIR™ HFA Inhalation Aerosol

Active Ingredient: fluticasone propionate/salmeterol xinafoate

Strengths: fluticasone propionate 44mcg/salmeterol xinafoate 30.45mcg
(equivalent to 21 mcg salmeterol base)
fluticasone propionate 110mcg/salmeterol xinafoate 30.45mcg
(equivalent to 21 mcg salmeterol base)
fluticasone propionate 220mcg/salmeterol xinafoate 30.45mcg
(equivalent to 21 mcg salmeterol base)

Dosage Form: inhalation aerosol

Route of Administration: oral inhalation

Please list the following patents in the U.S. Department of Health and Human Services "Orange Book" of Approved Drug Products.

	US Patent Number	Expiration Date	Form of Patent Claims
1	4,992,474	12 February, 2008	Drug Substance Method of Use
2	5,225,445	12 February, 2008	Method of Use
3	5,126,375	12 February, 2008	Drug Substance Drug Product
4	4,335,121	14 November, 2003	Drug Substance
5	5,270,305	7 September, 2010	Drug Substance
6	5,658,549	19 August, 2014	Drug Product Method of Use
7	5,674,472	7 October, 2014	Drug Product

The undersigned declares the following:

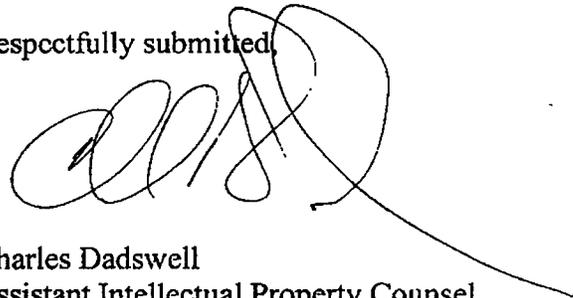
- 1) All of the above patents are owned by Glaxo Group Limited.
- 2) The United States Agent for Glaxo Group Limited is Glaxo Wellcome Inc.

- 3) The above Patents (4,335,121; 4,992,474; 5,225,445; 5,126,375, 5,270,305, 5,658,549 and 5,674,472) are required to be the subject of a submission of information pursuant to 21 C.F.R. §314.53(b), and meet the criteria for submission therein.
- 4) The above Patents (4,335,121; 4,992,474; 5,225,445; 5,126,375, 5,270,305, 5,658,549 and 5,674,472) cover the Drug Substance, Drug Product and/or Method of Use of ADVAIR™ HFA Inhalation Aerosol. This product is the subject of this application for which approval is being sought.

Please address all communications regarding the patent property of this NDA to:

David J. Levy
Vice President, Intellectual Property Counsel
Glaxo Wellcome Inc.
Intellectual Property Department
Five Moore Drive
Research Triangle Park, NC 27709
919/ 483-2723

Respectfully submitted,



Date: 6 November, 2000

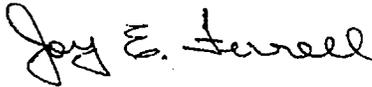
Charles Dadswell
Assistant Intellectual Property Counsel
Glaxo Wellcome Inc.
Registered Patent Attorney
Registration No. 35,851

Addendum:

Patents 4,992,474; 5,225,445; and 5,658,549 contain 'method of use' claims. For purposes of inclusion of patent information in the *Orange Book*, 'method of use' is defined as:

US Patent Number	Method of Use Description
4,992,474	Use in patients with reversible airway obstruction
5,225,445	Use in patients with reversible airway obstruction
5,658,549	Treatment of respiratory disorders

Signed



.....
Joy E. Ferrell
Director, Regulatory Affairs
Glaxo Wellcome Inc.

EXCLUSIVITY SUMMARY

NDA # 21-254

SUPPL #

HFD #

Trade Name Advair HFA Inhalation Aerosol

Generic Name fluticasone propionate and salmeterol xinafoate HFA inhalation aerosol

Applicant Name GlaxoSmithKline (GSK)

Approval Date, If Known June 8, 2006

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# Advair Diskus NDA 21- Flovent CFC and HFA NDA 20-548 and 21-433
077

NDA# Flovent Diskus NDA Flovent Rotadisk 20-549
20-833

NDA# Serevent Diskus and Flonase NDA 20-121
Serevent MDI NDA 20-
692, _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

SAS30001, SAS30003, SAS30004, SFCB3023

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a

Explain:

! Explain:

Investigation #2

!

YES

! NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

Name of person completing form: Ladan Jafari

Title: Regulatory Health Project Manager

Date: June 7, 2006

Name of Office/Division Director signing form: Division of Pulmonary & Allergy Products, Badrul Chowdhury, M.D., Ph.D.

Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

NDA 21-254

Fluticasone Propionate/Salmeterol Inhalation Aerosol

Request for Marketing Exclusivity

Pursuant to Section 505(c)(3)(D)(iii) and 505(j)(5)(D)(iii) of the Federal Food, Drug, and Cosmetic Act and Section 314.108(b)(4) of Title 21 of the Code of Federal Regulations, Glaxo Wellcome, Inc. requests three years of exclusivity from the date of approval of fluticasone propionate/salmeterol inhalation aerosol 44mcg/21mcg, 110mcg/21mcg, and 220mcg/21mcg for the maintenance treatment of asthma in patients 12 years of age and older.

Glaxo Wellcome, Inc. is entitled to such exclusivity as this application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by Glaxo Wellcome, Inc. The following investigations are "essential to the approval of the application" in that the application could not be approved by FDA without the following investigations:

Indication – Long-term, twice-daily maintenance treatment of asthma in patients 12 years of age and older

SAS30001: A Randomized, Double-Blind, Active-Controlled, Parallel-Group, 12-Week Trial Evaluating the Safety and Efficacy of the Salmeterol/Fluticasone Propionate Combination in GR106642X MDI, 42/88mcg BID, and Salmeterol in Propellant 11/12 MDI, 42mcg BID, and Fluticasone Propionate in Propellant 11/12 MDI, 88mcg BID, in Adolescent and Adult Subjects with Asthma (Report No. RM2000/00002/00)

SAS30003: A Stratified, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group 12-Week Trial Evaluating the Safety and Efficacy of the Salmeterol/Fluticasone Propionate Combination in GR106642X MDI, 42/88mcg BID, and Salmeterol in Propellant 11/12 MDI, 42mcg BID, Fluticasone Propionate in Propellant 11/12 MDI, 88mcg BID, and Placebo Propellant GR106642X MDI in Adult and Adolescent Subjects with Asthma (Report No. RM2000/00080/00)

SAS30004: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group 12-Week Trial Evaluating the Safety and Efficacy of the Salmeterol/Fluticasone Propionate Combination in GR106642X MDI, 50/250mcg BID, and Salmeterol in Propellant 11/12 MDI, 50mcg BID, and Fluticasone Propionate in Propellant 11/12 MDI < 250mcg BID, and Placebo in Propellant GR106642X MDI in Adolescent and Adult Subjects with Asthma (Report No. RM2000/00104/00)

SAS30005: A 12-Month, Open-Label, Stratified Study to Assess the Long-Term Safety of Salmeterol/Fluticasone Propionate/GR106642X Inhalation Aerosol at Doses of 50/100mcg, 50/250mcg, and 50/500mcg BID in Adolescent and Adult Subjects with Asthma (Report No. RM2000/00204/00)

NDA 21-254: ADVAIR™
(fluticasone propionate/salmeterol)
Inhalation Aerosol 44mcg/21mcg, 110mcg/21mcg,
and 220mcg/21mcg

New Drug Application: Maintenance Treatment of Asthma
in Patients 12 Years of Age and Older

DEBARMENT CERTIFICATION

Glaxo Wellcome hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.



Charles E. Mueller
Head, North American Clinical Compliance
World Wide Compliance

11-NOV-2000

Date

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-254 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: December 8, 2005 Action Date: June 8, 2006

HFD 570 Trade and generic names/dosage form: Advair HFA (fluticasone propionate and salmeterol xinafoate)
Inhalation Aerosol

Applicant: GSK Therapeutic Class: Respiratory

Indication(s) previously approved: None

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Asthma

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

xNo: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. 0 yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 4 Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

X Other: Formulation not appropriate for this age group.

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. 4 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 11 Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: GSK is developing the product for children-and do not expect to be completed with the program until at least 2007.

Date studies are due (mm/dd/yy): December 2007

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. >12 years Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-254
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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

/s/

Ladan Jafari

2/23/2006 02:22:58 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-254	Efficacy Supplement Type SE-	Supplement Number	
Drug: Advair HFA Inhalation Aerosol		Applicant: GSK	
RPM: Ladan Jafari		HFD-570	Phone # 301-796-1231
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed and/or corrected</p>		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):	
❖ Application Classifications:			
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority	
• Chem class (NDAs only)		3S	
• Other (e.g., orphan, OTC)		N/A	
• User Fee Goal Dates		June 8 2006	
❖ Special programs (indicate all that apply)			
		<input checked="" type="checkbox"/> None <input type="checkbox"/> Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2	
❖ User Fee Information			
• User Fee		<input checked="" type="checkbox"/> Paid UF ID number	
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)	
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)	
Application Integrity Policy (AIP)			
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? () Yes () No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? () Yes () No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> • Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	See attached Exclusivity summary
<ul style="list-style-type: none"> • Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	() Yes, Application # _____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	N/A

Actions	
<ul style="list-style-type: none"> Proposed action 	(X) AP () TA () AE () NA
<ul style="list-style-type: none"> Previous actions (specify type and date for each action taken) 	AE October 19, 2001, AE October 16, 2002
<ul style="list-style-type: none"> Status of advertising (approvals only) 	(X) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
<ul style="list-style-type: none"> Press Office notified of action (approval only) 	() Yes (X) Not applicable
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	(X) None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
<ul style="list-style-type: none"> Division's proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> Most recent applicant-proposed labeling 	June 7, 2006
<ul style="list-style-type: none"> Original applicant-proposed labeling 	December 20, 2000
<ul style="list-style-type: none"> Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings) 	May 31, 2006, 5/19, 2006, and 5/16/2006
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling) 	
❖ Labels (immediate container & carton labels)	
<ul style="list-style-type: none"> Division proposed (only if generated after latest applicant submission) 	
<ul style="list-style-type: none"> Applicant proposed 	2/17/06
<ul style="list-style-type: none"> Reviews 	
❖ Post-marketing commitments	
<ul style="list-style-type: none"> Agency request for post-marketing commitments 	See attached (pediatric)
<ul style="list-style-type: none"> Documentation of discussions and/or agreements relating to post-marketing commitments 	
<ul style="list-style-type: none"> Outgoing correspondence (i.e., letters, E-mails, faxes) 	See attached
<ul style="list-style-type: none"> Memoranda and Telecons 	See attached
❖ Minutes of Meetings	
<ul style="list-style-type: none"> EOP2 meeting (indicate date) 	
<ul style="list-style-type: none"> Pre-NDA meeting (indicate date) 	
<ul style="list-style-type: none"> Pre-Approval Safety Conference (indicate date; approvals only) 	
<ul style="list-style-type: none"> Other 	
❖ Advisory Committee Meeting	
<ul style="list-style-type: none"> Date of Meeting 	
<ul style="list-style-type: none"> 48-hour alert 	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	

Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	
	10/19/01, 10/17/01
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	9/30/02, 10/12/01, June 5, 2006
❖ Microbiology (efficacy) review(s) (indicate date for each review)	7/23/01
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	6/5/2006
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	2/23/06
❖ Demographic Worksheet (NME approvals only)	N/A
❖ Statistical review(s) (indicate date for each review)	9/21/2001
❖ Biopharmaceutical review(s) (indicate date for each review)	9/5/02, 10/5/01, 5/22/2006
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	10/4/01
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) (indicate date for each review)	5/23/2006, 3/7/06, 8/20/04, 10/18/01, 8/1/01
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	10/18/01
• Review & FONSI (indicate date of review)	N/A
• Review & Environmental Impact Statement (indicate date of each review)	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	7/23/01
❖ Facilities inspection (provide EER report)	Date completed: June 02, 2006 (X) Acceptable () Withhold recommendation
❖ Methods validation	() Completed (X) Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	10/19/01, 5/17/2006, 3/27/2006
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A

DATE JUNE 7, 2006

TOTAL 1
PAGES

To Ms. Ladan Jafari
Food and Drug Administration

FAX 301 796-9728
PHONE 301 796-1231

FROM Ms. Tracy L. Fischer, Pharm.D.

FAX 919 315-0033
PHONE 919 483-4223

Re: NDA 21-254; ADVAIR™ HFA (fluticasone propionate/salmeterol)
Inhalation Aerosol 45mcg/21mcg, 115mcg/21mcg, 230mcg/21mcg
General Memorandum: Labeling

[Handwritten marks consisting of several curved lines, possibly representing initials or a signature.]

Please contact me a (919) 483-4223 with any comments or questions concerning this facsimile.

The information contained in these documents is confidential and may also be privileged and is intended for the exclusive use of the addressee designated above. If you are not the addressee any disclosures, reproduction, distribution, or any other dissemination or use of this communication is strictly prohibited. If you have received this transmission in error please contact us immediately by telephone so that we can arrange for its return.

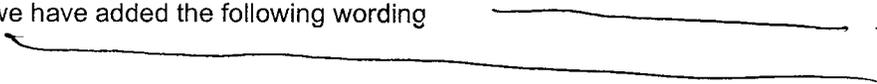
Jafari, Ladan

From: tracy.l.fischer@gsk.com
Sent: Wednesday, June 07, 2006 5:08 PM
To: Jafari, Ladan
Subject: Advair HFA labeling
Importance: High
Attachments: intermediate.pdf; carton.pdf; contain.pdf; emfinfo.txt

Hi Ladan,

Enclosed are the Advair HFA 45/21 trade overwrap label, trade canister and trade carton. The labeling for the sample 45/21 and the trades and samples for 115/21 and 230/21 strengths will look the same as the labeling I have attached to this email.

In addition, we have added the following wording



I will send the a PDF of the foil overwrap in a few minutes.

Thank you,
Tracy

Tracy Fischer, Pharm.D.
US Regulatory Affairs
GlaxoSmithKline
Phone: 919-483-4223
Fax: 919-315-0033

(A)

23 Page(s) Withheld

 Trade Secret / Confidential

 ✓ Draft Labeling

 Deliberative Process

Additional Labeling Comments to the Applicant June 5, 2006

NDA 21-254 - Advair HFA

DMETS consult received June 1, 2006

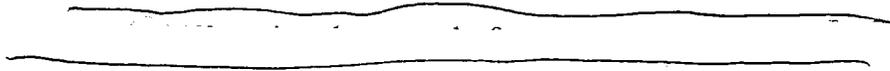
Consult recommendations reviewed by: Lydia Gilbert-McClain, MD, Medical Team leader and Craig Bertha, PhD, CMC reviewer

COMMENTS TO BE SENT TO THE APPLICANT

GENERAL COMMENTS

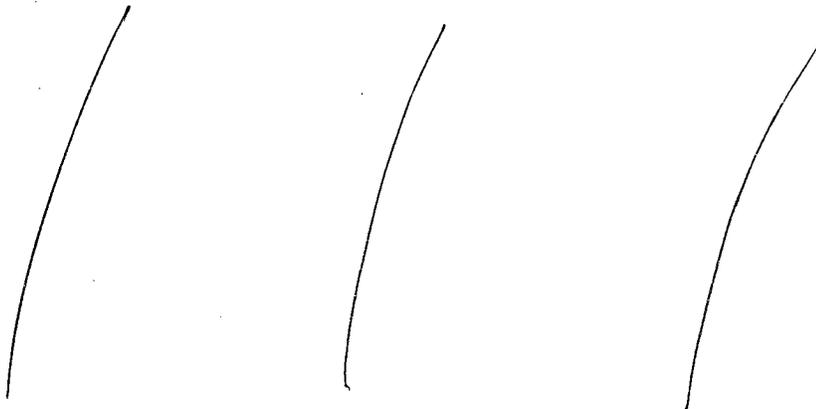
1. The labeling for Advair HFA is very similar to the labeling of Advair Diskus. This similarity may lead to confusion within the Advair HFA line and between Advair HFA and Advair Diskus. Differentiate the labels and labeling (e.g., using different colors, different fonts, trade dress, etc.) for the two products.

2.



3. Since patients taking Advair Diskus may be changed to Advair HFA, it is important that healthcare providers and patients understand the difference between the two products because the dose for Advair Diskus and Advair HFA are different. Therefore, In order to avoid underdosing or overdosing we recommend that you educate practitioners and patients on the differences between the two products and how to switch between them.

The following comments pertain to the CONTAINER LABEL (Sample label and Trade label)



13

2 Page(s) Withheld

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/s/

Lydia McClain
6/5/2006 11:43:29 AM
MEDICAL OFFICER



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: June 5, 2006

To: Tracy Fischer	From: Ladan Jafari
Company: GSK	Division of Pulmonary and Allergy Products
Fax number: 919-315-0033	Fax number: 301-796-9728
Phone number: 919-483-4223	Phone number: 301-796-1231
Subject: NDA 21-254	

Total Number of Pages Including Cover: 4

Comments: Labeling comments

Document to be mailed: YES NO

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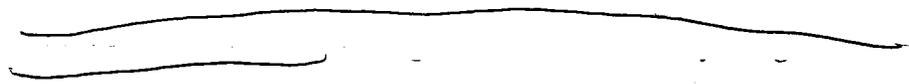
Dear Dr. Fischer:

We are reviewing the labeling for Advair HFA and have the following comments. Please respond to these requests by COB on June 6, 2006.

GENERAL COMMENTS

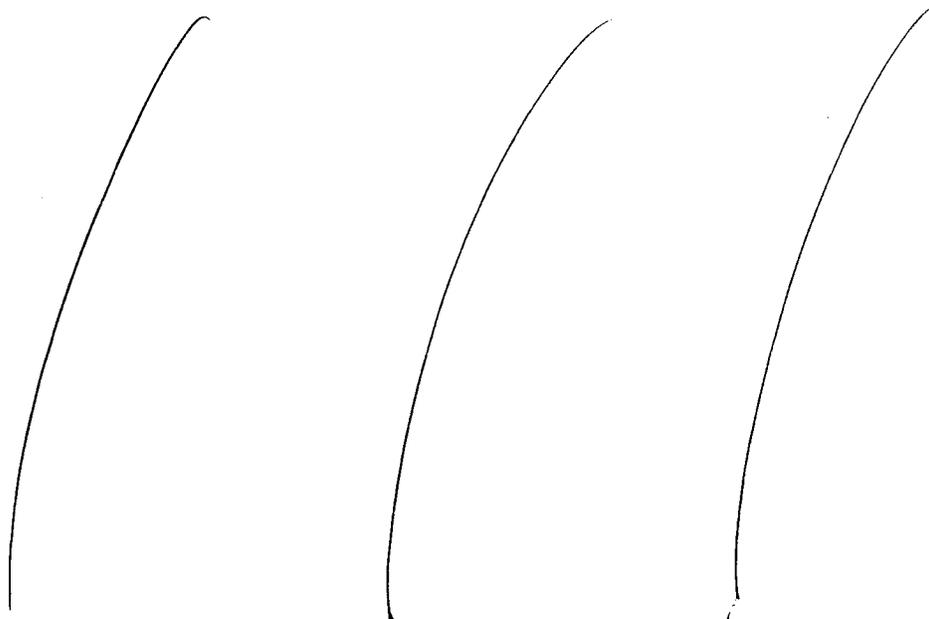
1. The labeling for Advair HFA is very similar to the labeling of Advair Diskus. This similarity may lead to confusion within the Advair HFA line and between Advair HFA and Advair Diskus. Differentiate the labels and labeling (e.g., using different colors, different fonts, trade dress, etc.) for the two products.

2.



3. Since patients taking Advair Diskus may be changed to Advair HFA, it is important that healthcare providers and patients understand the difference between the two products because the dose for Advair Diskus and Advair HFA are different. Therefore, in order to avoid underdosing or overdosing we recommend that you educate practitioners and patients on the differences between the two products and how to switch between them.

The following comments pertain to the CONTAINER LABEL (Sample label and Trade label)



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NDA 21-254
Page 3

I may be reached at 301-796-1231 for any questions.

Ladan Jafari, Regulatory Health Project Manager

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/s/

Ladan Jafari
6/5/2006 02:27:46 PM
CSO



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: May 30, 2006

To: Tracy Fischer	From: Ladan Jafari
Company: GSK	Division of Pulmonary and Allergy Products
Fax number: 919-315-0033	Fax number: 301-796-9728
Phone number: 919-483-4223	Phone number: 301-796-1231
Subject: NDA 21-254	

Total Number of Pages Including Cover: 15

Comments: Labeling comments

Document to be mailed: YES NO

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Ladan Jafari
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Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: May 17, 2006

To: Sue Holmes	From: Ladan Jafari
Company: GSK	Division of Pulmonary and Allergy Products
Fax number: 919-483-5381	Fax number: 301-796-9728
Phone number: 919-483-4411	Phone number: 301-796-1231

Subject: NDA 21-254

Total Number of Pages Including Cover: 3

Comments: CMC Comments

Document to be mailed: YES NO

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NDA 21-254

Dear Ms. Holmes:

We are reviewing your NDA submission for Advair HFA and we request that you submit your agreements to the following requests by May 22, 2006.

1. Agree that efforts will be made to examine the and to minimize it if possible, file any associated changes according to Agency guidance, and provide brief summaries of any progress in annual reports.
2. Agree to re-evaluate the Parametric Tolerance Interval Test approach for dose content uniformity once an adequate database is available (i.e., approximately 18 months after product launch), and _____
3. Agree to submit the _____
4. Agree that post-approval agreements and subsequent changes and filing mechanisms outlined in the May 14, 2004, approval letter for the Flovent HFA Inhalation Aerosol application (N21-433) will also apply to the Advair HFA application in cases where there is commonality of the chemistry, manufacturing, and controls.

I may be reached at 301-796-1231 for any questions.

Ladan Jafari, Regulatory Health Project Manager

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/s/

Ladan Jafari
5/17/2006 01:12:07 PM
CSO



NDA 21-254

DISCIPLINE REVIEW LETTER

GlaxoSmithKline
P. O. Box 13398
5 Moore Drive
Research Triangle Park, No 27709-3398

Attention: Sue M. Holmes, MS
Assistant Director, CMC Regulatory Affairs

Dear Ms. Holmes:

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

We also refer to your submission dated September 12, 2002, June 7 and December 7, 2005, and February 17, 2006.

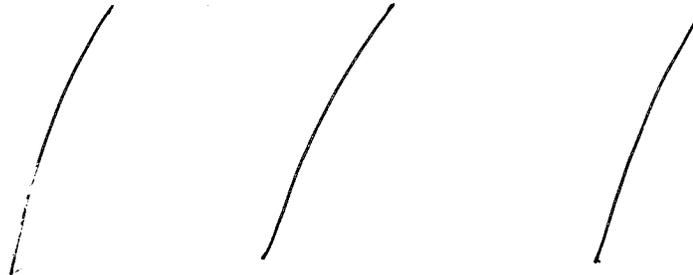
Our review of the Chemistry, Manufacturing and Controls section of your submission is complete, and we have identified the following deficiencies:

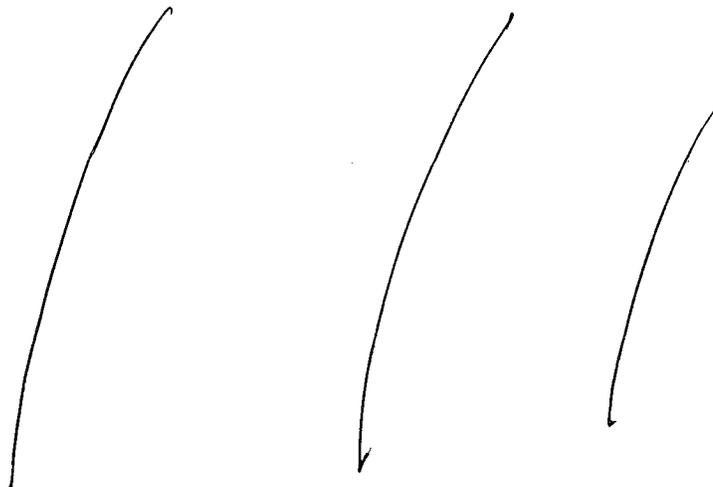
We request that you provide your agreements with comments 1 and 2 listed below:

1. Although the changes made to the container closure system of the product appear to have provided some improvement in the stability _____
_____, the _____ has become more pronounced _____). Study ways in which this _____ can be reduced for the product, discuss filing mechanisms for the implementation of any such improvements with the Agency as necessary, and provide a brief summary of progress in annual reports.
2. Revise the dose content uniformity acceptance criteria for the Advair HFA drug product by adopting the parametric tolerance interval test (PTIT) approach once it is agreed upon by IPAC-RS and the Agency.

3. DMF _____ was reviewed and was found to be inadequate with respect to a supporting DMF. A deficiency letter has been forwarded to the holder. Once the holder responds completely to the deficiency letter by amendment of the DMF, provide the Agency with the date of that complete response.
4. DMF _____ was reviewed _____ to be used in the _____ and was found to be inadequate to support your application. A deficiency letter was forwarded to the holder. Once the holder completely responds to the deficiency letter, include the date of the DMF amendment in your response to this comment.
5. DMF _____ was reviewed _____ to be used _____ and was found to be inadequate to support your application. A deficiency letter was forwarded to the holder. Once the holder completely responds to the deficiency letter, include the date of the DMF amendment in your response to this comment.
6. An expiration dating period of _____ months is not supported by your current limited stability data and associated statistical analysis. However, consideration has been given to your arguments in P.9.4.1.2 and 12 months can be granted at this time until updated data with a statistical analysis can be shown to fully support a longer expiry.
7. Revise the in-use stability protocol such that _____

8. Submit a separate correspondence (electronic) that includes an up-to-date methods validation package for the drug product that includes the following: 1) tabular list of samples (and necessary reference standards) with lot number, identity, date of manufacture, and quantity indicated; 2) final drug product analytical procedures; 3) validation data supporting the individual analytical procedures; 4) analytical results for the batches of drug product for which samples are submitted using the methods described; 5) the components and composition of the drug product; 6) specifications for the drug product; 7) material safety data sheets (MSDSs) for all samples, standards, and reagents.
9. The following are preliminary labeling comments. Submit draft labeling and mock-ups incorporating the following revisions.





Additional comments may be forthcoming regarding your response to comment 3 of the October 2, 2002, approvable letter and the leachable 1,3,5-trioxane.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Ms. Ladan Jafari, Regulatory Project Manager, at 301-796-1231.

Sincerely,

Blair A. Fraser, Ph.D
Chief, Branch 2
Division of Pre-Marketing Assessment 1
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Blair Fraser
3/9/2006 09:04:50 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION REQUEST

TO: FDA
Division of Pharmaceutical Analysis, HFD-920
Attn: Nick Westenberger
Room 1002
1114 Market Street
St. Louis, MO 63101

FROM: Craig M. Bertha, Ph.D., Reviewing Chemist
E-mail Address: craig.bertha@fda.hhs.gov
Phone: (301)-796-1646
Fax.: (301)-796-9747

Through: Blair Fraser, Ph.D., Branch Chief, Branch II
Phone: (301)-796-1671

and

Michael Folkendt, ONDC Methods Validation Coordinator, ONDQA
Phone: 301-796-1670

SUBJECT: Methods Validation Request

Application Number: NDA 21-254

Name of Product: Advair HFA (fluticasone propionate/salmeterol) Inhalation Aerosol

Applicant: Glaxo Group Ltd. d/b/a GlaxoSmithKline

Applicant's Contact Person: Tracy L. Fischer, Manager, US Reg. Affairs

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

Telephone: (919) 483-4223 Fax:

Date NDA Received by CDER: **12/20/2000**
glucocorticoid/LABA

Chemical/Therapeutic Type:

Date of Amendment(s) containing the MVP: **12/7/2005**

Special Handling Required: No

DATE of Request: **May 4, 2006**

DEA Class: N/A

Requested Completion Date: **9/7/2006**

Format of Methods Validation Package

PDUFA User Fee Goal Date: **6/7/2006**

Paper Electronic Mixed

We request suitability evaluation of the proposed manufacturing controls/analytical methods as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request Form*. Upon receipt of the samples, perform the tests indicated in item 3 of the attached *Methods Validation Request Form* as described in the MV package. We request your report to be submitted in DFS promptly upon completion, but not later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. If the requested completion date cannot be met, please promptly notify the reviewing chemist and the ONDC Methods Validation Coordinator.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying Methods Validation Report Summary). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by the director via DFS. Send the complete report, with the DFS signed *Methods Validation Report Summary*, by overnight courier to the above reviewing chemist. All information relative to this application is to be held confidential as required by 21 CFR 314.430.

ATTACHMENT(S): *Methods Validation Request Form*, NDA Methods Validation Package (if not available in the EDR).

(E)

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/s/

Michael Folkendt
5/5/2006 04:39:02 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-254

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

Attention: Tracy L. Fischer, Pharm.D.
Manager, Regulatory Affairs

Dear Dr. Fischer:

We acknowledge receipt on December 8, 2005, of your December 7, 2005, resubmission to your new drug application for Advair HFA (fluticasone propionate and salmeterol xinafoate) Inhalation Aerosol.

We consider this a complete, class 2 response to our October 16, 2002, action letter. Therefore, the user fee goal date is June 8, 2006.

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. We note that you have not fulfilled the requirement. We are deferring submission of your pediatric studies until December 8, 2007. 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.

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 section 2 of the Pediatric Research Equity Act (PREA) 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" in addition to your plans for pediatric drug development described above. Please note that satisfaction of the requirements in section 2 of PREA alone may not qualify you for pediatric exclusivity.

NDA 21-254
Page 2

If you have any question, call Ms. Ladan Jafari, Regulatory Project Manager, at (301) 796-1231.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Chief Project Management Staff
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Ladan Jafari
1/13/2006 11:16:54 AM
Signed for Sandy Barnes.



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: October 26, 2004

To: Sue Holmes	From: Ladan Jafari
Company: GSK	Division of Pulmonary and Allergy Drug Products
Fax number: 919-483-5381	Fax number: 301-827-1271
Phone number: 919-483-4411	Phone number: 301-827-1084

Subject: NDA 21-254

Total no. of pages including cover: 5

Comments: Meeting minutes

Document to be mailed: YES NO

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NDA 21-254
Drug: Advair HFA
Applicant: GSK
Date of Telecon: October 18, 2004
IMTS: 13708

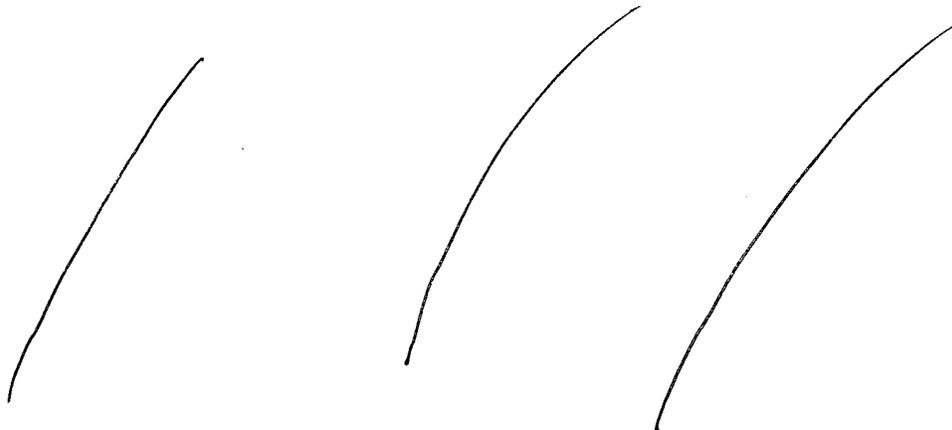
GSK Representatives:

Michael Golden, Director, CMC Regulatory Affairs
Sue Holmes, Assistant Director, CMC Regulatory Affairs
Charlie Mader, Director, Inhalation Product Development
John Miller, Manager (ADV AIR HFA), Inhalation Product Development
Ian Ashurst, Director, New Product Supply
Bob Wylie, Head of Quality Control
Loy Britto, Director, Inhalation Product Development
Jackie West, Manager (MDI-Counter), Inhalation Product Development

Division of Pulmonary & Allergy Drug Products (DPADP) Representatives:

Alan Schroeder, CMC Reviewer
Richard Lostritto, CMC Team Leader
Ladan Jafari, Regulatory Project Manager

Background: GSK Submitted a meeting request dated July 19, 2004, to discuss the results of particle size distribution by cascade impaction for Advair HFA. GSK also submitted a briefing package dated August 2, 2004, which had a list of questions to be discussed at this meeting. Upon review of the package the Division responded to GSK's questions via telephone facsimile on October 14, 2004. The content of this telephone facsimile is printed below in *Italics*. Upon receipt of this telephone facsimile, GSK requested that the Division clarify the responses to questions 1 and 2 via a teleconference, and cancel the face to face meeting originally scheduled. Any discussions relevant to questions 1 and 2 are printed in regular font under each response.



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NDA 21-254
Drug: Advair HFA
Applicant: GSK
Date of Telecon: October 18, 2004
IMTS: 13708
Page 5

Drafted by: LJ/10-21-04

Initialed by: Schroeder/10-26-04
Lostritto/10-26-04

Filename: N21254tconmin.doc



Food and Drug Administration
Center for Drug Evaluation and
Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: October 14, 2004

To: Sue Holmes	From: Ladan Jafari
Company: GSK	Division of Pulmonary and Allergy Drug Products
Fax number: 919-483-5381	Fax number: 301-827-1271
Phone number: 919-483-4411	Phone number: 301-827-1084
Subject: NDA 21-254	

Total no. of pages including cover: 5

Comments: CMC Comments

Document to be mailed: YES NO

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NDA 21-254

Dear Ms. Holmes:

Attached are our responses to the questions listed in your August 2, 2004, background package. You have the option of canceling the meeting scheduled for October 18, 2004, if these responses are clear to you. If you choose to have the meeting, we will be prepared to clarify any questions that you have regarding our responses.

Please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, nor reach agreement on such changes at the meeting. Any modification to the development plan, for which you would like FDA feedback, should be submitted as a new meeting request. Please let me know as soon as possible if you are canceling the meeting or if you would like to have a teleconference instead.

I can be reached at 301-827-1084 for any questions.


Ladan Jafari, Regulatory Project Manager

(G)

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Ladan Jafari
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: August 26, 2004

To: Sue Holmes	From: Ladan Jafari
Company: GSK	Division of Pulmonary and Allergy Drug Products
Fax number: 919-315-483-5381	Fax number: 301-827-1271
Phone number: 919-483-4411	Phone number: 301-827-1084
Subject: NDA 21-254	

Total no. of pages including cover: 2

Comments: CMC Comments

Document to be mailed: YES NO

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NDA 21-254

Dear Ms. Holmes:

We have performed a preliminary review of your proposed new stability protocol. Note that this review was not performed with consideration of all outstanding issues for this NDA, which should be considered before proceeding with the stability study. We have the following comments and requests for information.

1. Explain the following comment pertaining to the proposed core stability protocol (pg.20): "This protocol may be modified in view of the data as they are generated."
2. Acceptance criteria for leachables in the drug product should be based upon your stability data. If your long term stability studies for leachables are conducted at _____ then the acceptance criteria should be based upon stability data obtained after storing under these conditions. Similarly, a safety assessment should be provided for these data, and an extractables/leachables correlation should be established.
3. Measure the parameter, foreign particulates, at the _____ time point for storage at 25°C/60% RH as well as at the proposed time points.
4. Add leachables testing at the _____ time point (_____ storage conditions) and at the _____ time point (_____ storage conditions).
5. The stability protocol should include modifications based upon our comments pertaining to drug product specifications, in accordance with our last approvable letter (October 16, 2002).
6. We note that leachables specifications have not yet been proposed and reviewed in accordance with this NDA.
7. When reporting results of the stability study, provide a comparison with previous stability data, including appropriate summary graphs and tables.

I can be reached at 301-827-1084 for any questions.

Ladan Jafari, Regulatory Project Manager

NDA 21-254

Page 2

Initialed by: Barnes/8-25-04
Schroeder/8-26-04
Lostritto/8-26-04

Filename:N21254CMCcomments.doc

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/s/

Ladan Jafari
8/26/04 04:41:53 PM
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Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: March 5, 2003

To: Debra Lake	From: Ladan Jafari
Company: GSK	Division of Pulmonary and Allergy Drug Products
Fax number: 919-315-4364	Fax number: 301-827-1271
Phone number: 919-483-9500	Phone number: 301-827-1084
Subject: Advair HFA	

Total no. of pages including cover: 7

Comments:

Document to be mailed: YES NO

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NDA 21-254
Drug: Advair HFA Inhalation Aerosol
Applicant: GlaxoSmithKline (GSK)
Meeting Date: February 10, 03
IMTS: 9683

GSK Representatives:

Alan Cripps, Ph.D., Director, MDI Development
Alan Colborn, Ph.D., Director, Quality Control
Michael Golden, Ph.D., Director, CMC Regulatory Affairs
Debra Lake, Assistant Director, CMC Regulatory Affairs
Charles Mader, Ph.D., Director, Head Inhalation Product Development
Michael Riebe, Ph.D., Director, New Product Supply
Robert Schultz, Advair Project Team Leader

Division of Pulmonary & Allergy Drug Products (DPADP):

Alan Schroeder, Ph.D., CMC Reviewer
Guirag Poochikian, Ph.D., CMC Team Leader
Ladan Jafari, Regulatory Project Manager
Badrul Chowdhury, M.D., Ph.D., Acting Director

Office of New Drug Chemistry:

Eric Duffy, Ph.D., Director

Background: On December 3, 2002, GSK requested a meeting to discuss the approvable letter of October 16, 2002, for Advair HFA. GSK submitted a briefing package dated December 20, 2002, containing a few questions to be discussed at this meeting followed by an additional question dated January 24, 2003, regarding the — process.

The Division initiated the meeting by acknowledging the fact that there were quite a number of deficiencies cited in the approvable letter dated October 16, 2002, however, the number of questions that GSK asked to clarify were only a few. The Division indicated that it is our impression that GSK fully understands the remaining issues and will respond adequately to the above approvable letter. The Division indicated that we are trying to avoid multiple review cycles for this application. GSK responded that they believe they understand the remaining questions of the approvable letter and they too do not wish to delay the approval of this application. The comments from the approvable letter that GSK wished to discuss were numbers 3, 6.b., 6.e., 7.c.(1), 7.g., 7.l., and 8.d.

(H)

5 Page(s) Withheld

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NDA 21-254
Drug: Advair HFA
Applicant: GlaxoSmithKline (GSK)
Meeting Date: February 10, 03
IMTS: 9683
Page 7

Drafted by: LJ/2-14-03

Initialed by: Schroeder/2-28-03
Poochikian3-3-03
Chowdhury/3-4-03

Filename: N21254mtgmin.doc

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/s/

Ladan Jafari
3/5/03 11:03:26 AM
CSO



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: August 2, 2002

To: Ms. Sue Holmes	From: Ladan Jafari
Company: GSK	Division of Pulmonary and Allergy Drug Products
Fax number: 919-483-5381	Fax number: 301-827-1271
Phone number: 919-483-4411	Phone number: 301-827-1084

Subject: NDA 21-254

Total no. of pages including cover: 2

Document to be mailed: YES NO

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Thank you.



NDA 21-254

In response to your telephone facsimile of July 19, 2002, we have the following comments.

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.

If you have any questions, I may be reached at 301-827-1084.

Ladan Jafari, Regulatory Project Manager

NDA 21-254

Initialed by: Barnes/8-2-02
Schroeder/8-2-02
Poochikian/8-2-02

Filename: N21254Augcomments

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/s/

Ladan Jafari
8/2/02 02:32:39 PM
CSO



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: June 14, 2002

To: Ms. Sue Holmes	From: Ladan Jafari
Company: GSK	Division of Pulmonary and Allergy Drug Products
Fax number: 919-483-5381	Fax number: 301-827-1271
Phone number: 919-483-4411	Phone number: 301-827-1084
Subject: NDA 21-254	

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES NO

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We are reviewing your NDA resubmission for Advair HFA Inhalation Aerosol and have the following requests for information.

1. Your proposed specifications for individual and mean dose content uniformity of the drug product are not adequate. Please see the draft MDI guidance for more information about the Agency's approach to this specification. This comment was previously addressed in comment 5e(1) of our letter dated October 19, 2001.
2. 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.
3. 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.
 - a. 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).
 - b. 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).

- c. 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.
 - d. 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.
4. In cases in which 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 extractable methods to increase the amounts of extractables obtained, such that they are more than the leachables.
 5. Clarify Tables 164 and 165, page 342-3 of Appendix 11 of your amendment dated 4/15/02, 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.

If you have any questions, please contact me at 301-827-1084.

Ladan Jafari, Regulatory Project Manager

NDA 21-254

Page 3

Initialed by: Barnes/6-14-02
Schroeder/6-14-02
Poochikian/6-14-02

Filename:N21254CMCinforequest

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/s/

Ladan Jafari
6/14/02 12:54:21 PM
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: May 28, 2002

To: Lorna Wilson/Robert Bohinsky	From: Ladan Jafari
Company: GSK	Division of Pulmonary and Allergy Drug Products
Fax number: 919-315-0033	Fax number: 301-827-1271
Phone number: 919-483-5121	Phone number: 301-827-1084
Subject: NDA 21-077 & 21-254	

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES NO

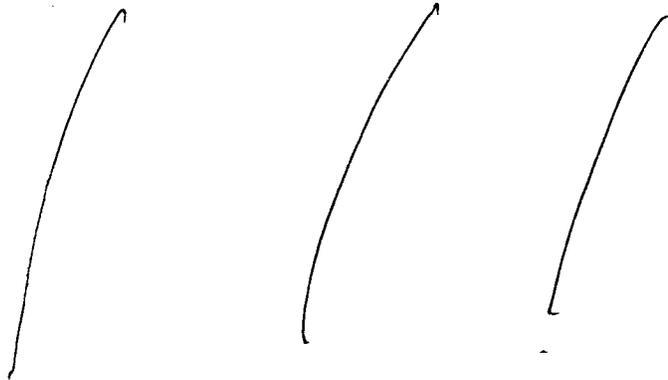
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NDA 21-254
NDA 21-077

We completed the review of your submission dated April 25, 2002, containing comments regarding the meeting minutes of February 19, 2002, and we have the following comments.

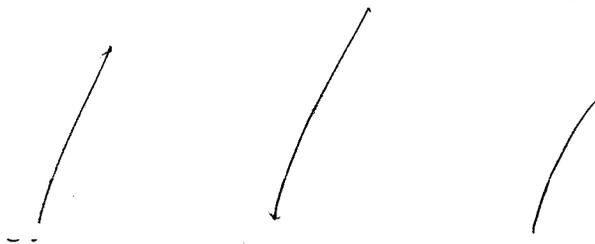
1.



2. This pertains to question 2 of your submission. Your position is noted. We will expect this submission.

3. This pertains to question 3 of your submission. Your position is noted. The Division is in agreement with GSK's description of the pediatric study endpoints and patient inclusion criterion stated in this response. We believe that the Agency's official minutes are reflective of both these points. This document will be used as an addendum to the meeting minutes to clarify this point.

4. This pertains to question 5 of your submission. Your position is noted. The



5. This pertains to the additional comment regarding



NDA 21-254

NDA 21-077

Page 2

If you have any questions, you may contact me at (301) 827-1084.

Ladan Jafari, Regulatory Project Manager

NDA 21-254

NDA 21-077

Page 3

Initialed by: Purucker/5-24-02

Fadiran/5-24-02

Meyer/5-24-02

Filename: GSK mtgmin addendum

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/s/

Ladan Jafari
5/28/02 08:54:30 AM



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: March 25, 2002

To: Ms. Sue Holmes	From: Ladan Jafari
Company: GSK	Division of Pulmonary and Allergy Drug Products
Fax number: 919-483-5381	Fax number: 301-827-1271
Phone number: 919-483-4411	Phone number: 301-827-1084
Subject: CMC comments for Advair HFA	

Total no. of pages including cover: 5

Comments:

Document to be mailed: YES NO

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We are providing the following preliminary comments (CMC) in order to facilitate your drug development program. These comments refer to your amendments dated June 29, and November 7, 2001. These comments are in addition to, but do not supercede CMC comments previously provided in our Approvable letter dated October 19, 2001, which should be adequately addressed.

1. The following comment pertains to your amendment dated November 7, 2001, which includes up to three months of stability data on drug product that was 100% heat-stressed during manufacture.

Provide an update of stability data for both _____ and _____ drug product batches, including appropriate summary data and graphs and comparative summary data for both types of drug product relative to _____. Provide an appropriate statistical comparison of _____.

2. You are reminded of our previous request for summary stability data and graphics, comparing stability of the batches of drug product manufactured with drug substance from different manufacturing and micronization sites. Reference is made to our letter of March 9, 2001 (Comment 2), your response in the amendment dated June 29, 2001, and our subsequent telephone conversations with you on this topic on January 8 and 10, 2002.

3. Clarify or reference the _____ procedure used in the ongoing stability study for the _____ product and provide or reference the stability protocol used. You are reminded of our concerns about the proposed _____ discussed in our meetings with you on June 8, 2001, and August 24, 2001. Address these issues and modify the master batch record accordingly.

4. The following comment pertains to comment 6c in our letter dated March 9, 2001 and pertains to the response in your Amendment dated June 29, 2001.

Provide an appropriate statistical comparison of _____.

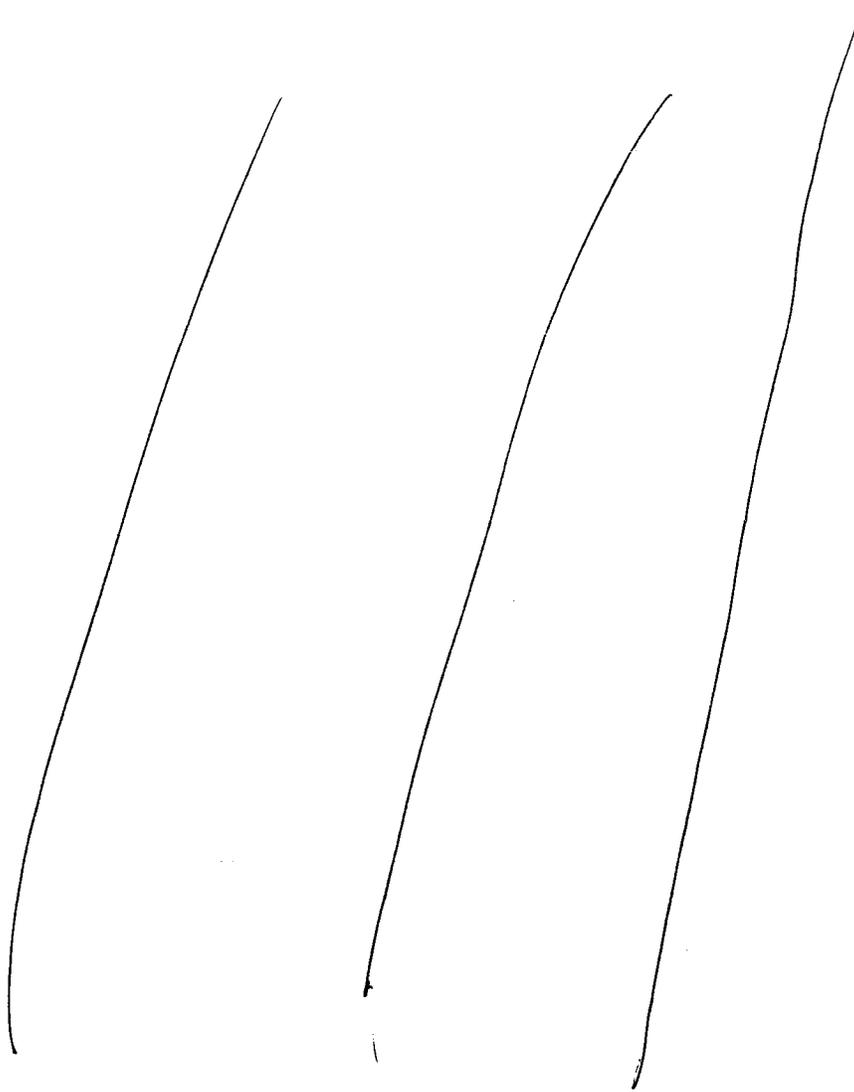
5. The following comment pertains to comment 6e in our letter dated March 9, 2001, to the response in your Amendment dated June 29, 2001, and to the revised protocol in your amendment dated June 5, 2001.

You are reminded that our comments about your previous _____ study remain in effect until the study is adequately repeated.

6. The following comment pertains to comment 6f in our letter dated March 9, 2001, and pertains to the response in your Amendment dated June 29, 2001.

You are referred to related comments in our Approvable letter dated October 19, 2001, e.g., including those pertaining to the _____ product's stability protocol and the post-approval stability protocol.

7. The following comments pertain to _____



8. The following comments pertain to stability data provided to date on drug product leachables. You are reminded particularly of comment #17 pertaining to the extractable/leachable correlation in our approvable letter dated October 19, 2001, and to our previous discussion of this issue (see our minutes of our meeting on February 4, 2002).

- a. Clarify why many _____ leachables appear at somewhat lower levels in the _____ samples (see Table 3 on page 4 in Appendix 6, in the June 29, 2001, amendment) than they did in the _____ samples (see page 172, Appendix 2, vol. 4.10 of original NDA). Provide an explanation, if possible, as to why this occurs.
- b. Explain why _____ leachable levels of _____, which were reported after _____ of storage (see original NDA), are lower than the value of the Limit of Quantitation reported with the _____ data (see the June 29, 2001, amendment).

9. Address the concerns brought up by the FDA in our meeting on February 4, 2002.

Review of stability data, including data on _____ drug product in your November 7, 2001, amendment, is deferred pending submission of updated stability data, agreement on drug product specifications, and responses to the requests in this letter. This also applies to review of the proposed expiration dating period for the drug product.

We also have the following additional comments in response to your telephone facsimile received on March 6, 2002.

10. The following comments are in response to the question as to whether there is an estimated date when GSK can expect comments on the information "that has not been fully reviewed to date" (see Table 3 of your submission dated November 21, 2001).
 - a. This pertains to information submitted as stability updates or in response to several requests for information made by telephone. Any comments on this information will be provided in the next review cycle, when stability data are summarized (as requested) and updated once more.

①

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NDA 21-254

Page 5

Initialed by: Barnes/3-14-02
Schroeder/3-25-02
Poochikian/3-25-02

Filename: AdvairCMC comments

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/s/

Ladan Jafari
3/25/02 01:52:08 PM
CSO



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Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: March 25, 2002

To: Ms. Lorna Wilson	From: Ladan Jafari
Company: GSK	Division of Pulmonary and Allergy Drug Products
Fax number: 919-315-0033	Fax number: 301-827-1271
Phone number: 919-483-5121	Phone number: 301-827-1084

Subject: Clinical comments for Advair Pediatric program

Total no. of pages including cover: 2

Comments:

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NDA 21-254
NDA 21-077
Page 2

Initialed by: Barnes/3-21-02
Purucker/3-21-02
Mann/3-21-02
Suarez/3-25-02
Fadiran/3-25-02

Filename: Advairpedscomments

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Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: March 19, 2002

To: Ms. Lorna Wilson	From: Ladan Jafari
Company: GSK	Division of Pulmonary and Allergy Drug Products
Fax number: 919-315-0033	Fax number: 301-827-1271
Phone number: 919-483-5121	Phone number: 301-827-1084
Subject: Meeting minutes of February 19, 2002	

Total no. of pages including cover: 10

Comments:

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NDA 21-254 Advair HFA
NDA 21-077 Advair Diskus
Sponsor: GlaxoSmithKline
Meeting Date: February 19, 2002
IMTS: 8077
Page 1

GlaxoSmithKline (GSK) Representatives:

Chai-Ni Chang, Ph.D., Senior Statistician
Paul Dorinsky, M.D., Sr. Director, Clinical Development Medical Affairs
Karen House, Director, Clinical Development Medical Affairs
Elaine Jones, Ph.D., Director, Regulatory Affairs
Robert L. Kunka, Ph.D., Section Head, Clinical Pharmacology & Discovery Medicine
Yonghua Wang, Ph.D., Manager, Exploratory & Full Development Statistics
Lorna Wilson, Director, Regulatory Affairs

Division of Pulmonary & Allergy Drug Products (DPADP) Representatives:

Emmanuel Fadiran, Ph.D., Clinical Pharmacology & Biopharmaceutics Team Leader
James Gebert, Ph.D., Biometrics Team Leader
Lydia Gilbert-McClain, M.D., Clinical Reviewer
Ladan Jafari, Regulatory Project Manager
Marianne Mann, M.D., Acting Division Director
Mary Purucker, M.D., Ph.D., Clinical Team Leader
Curtis Rosebraugh, M.D., Clinical Reviewer

Background: GSK submitted a meeting request dated November 19, 2001, to discuss the clinical program of Advair Diskus and Advair HFA in the pediatric population. This submission included a list of questions to be discussed at the meeting. GSK also submitted a second document dated February 11, 2002, which contained a presentation outlining the

The questions raised by GSK are printed in Italics below followed by the Division's responses and discussions. Please see Attachment 1 for Drs. Rosebraugh and Fadiran's slides.

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/s/

Ladan Jafari
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: February 28, 2002

To: Ms. Sue Rider	From: Ladan Jafari
Company: GSK	Division of Pulmonary and Allergy Drug Products
Fax number: 919-483-5381	Fax number: 301-827-1271
Phone number: 919-483-4411	Phone number: 301-827-5584
Subject: CMC meeting minutes	

Total no. of pages including cover: 6

Comments:

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NDA 21-254
Drug: Advair HFA
Applicant: GlaxoSmithKline
Meeting Date: February 4, 2002
IMTS: 8074

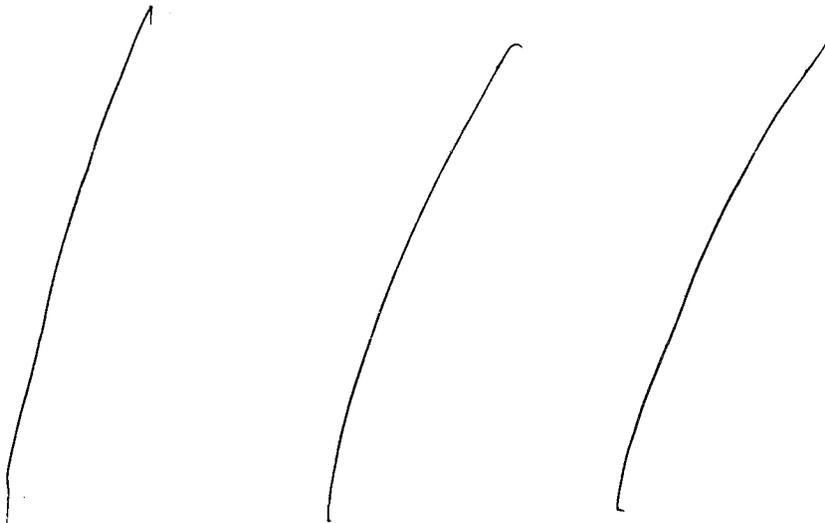
GlaxoSmithKline (GSK) representatives:

Alan Colborn, Ph.D., Director, Quality Control
Alan Cripps, Ph.D., Director, MDI Development
Charlie Mader, Ph.D., Director, Head Inhalation Product Development
Susan Rider, Msc., Assistant Director, Regulatory Affairs
Michael Reibe, Ph.D., Director, New Product Supply
Robert Schultz, Advair Project Team Leader
Satinder Sethi, Ph.D., Vice President, Inhaled Product Strategy

Division of Pulmonary & Allergy Drug Products (DPADP) representatives:

Ladan Jafari, Regulatory Project Manager
Robert Meyer, M.D., Director
Guirag Poochikian, Ph.D., Chemistry Team Leader
Alan Schroeder, Ph.D., Chemistry Reviewer

Background: GSK submitted a meeting request to the Division on November 21, 2001, to discuss a few of the deficiencies listed in the approvable letter dated October 19, 2001. The Division's responses and discussions of the meeting follow the question numbers as were outlined in the approvable letter.



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NDA 21-254
Drug: Advair HFA
Applicant: GlaxoSmithKline
Meeting Date: February 4, 2002
IMTS: 8074
Page 6

Initialed by: Schroeder/2-26-02
Poochikian/2-26-02

Filename: Advair mtgmin.doc

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/s/

Ladan Jafari
2/28/02 02:46:07 PM

Record of Telephone Conversation

Date: January 8, 2002
Subject: NDA 21-254
Initiated by: FDA
Product Name: Advair HFA Inhalation Aerosol
Firm Name: GSK
Contact: Ms. Sue Rider, Assistant Director, CMC QA
Telephone Number: 919-483-4411

I spoke with Ms. Rider about comment #2 in our previous IR letter dated March 9, 2001, and about their response in amendment dated June 29, 2001. This pertains to our request for a comparison in the form of drug product stability data and graphics, for drug product manufactured with drug substance from different manufacturing and micronization sites.

I said that their response included hundreds of pages of data. We again would like to ask for a more concise data summary (giving mean data and an indication of individual data variability). We are looking for a direct comparison of drug product stability data from the two manufacturing sites for the drug substance (salmeterol xinafoate), i.e. _____ and for the two drug substance micronization sites for both fluticasone propionate and salmeterol xinafoate (i.e., _____). The idea is to show equivalence of the drug product manufactured with drug substance produced (and micronized) at the various sites.

I indicated that their response will facilitate the review process.

Ms. Rider asked if they could combine batches in their summary. I said that this could be done as long as there is information about individual variability as well. Of course, some data should not be combined (e.g., that from different strengths of drug product).

She agreed to give it another try, and she will let me know the approximate time frame of the response.

I thanked her and this ended the conversation.

Alan C. Schroeder, Ph.D.

<p>cc: Orig. NDA #21-254 HFD-570/Division file HFD-570/ACSchroeder/1-08-02 HFD-570/GPoochikian HFD-570/CSO LJafari</p>	<p>R/D init. by: ACSfile: N21254_2002-01-08.doc</p>
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: October 16, 2001

To: Ms. Sue Rider	From: Ladan Jafari
Company: GlaxoSmithkline	Division of Pulmonary and Allergy Drug Products
Fax number: 919-483-5063	Fax number: 301-827-1271
Phone number: 919-483-4411	Phone number: 301-827-5584
Subject: CMC comments	

Total no. of pages including cover: 2

Comments:

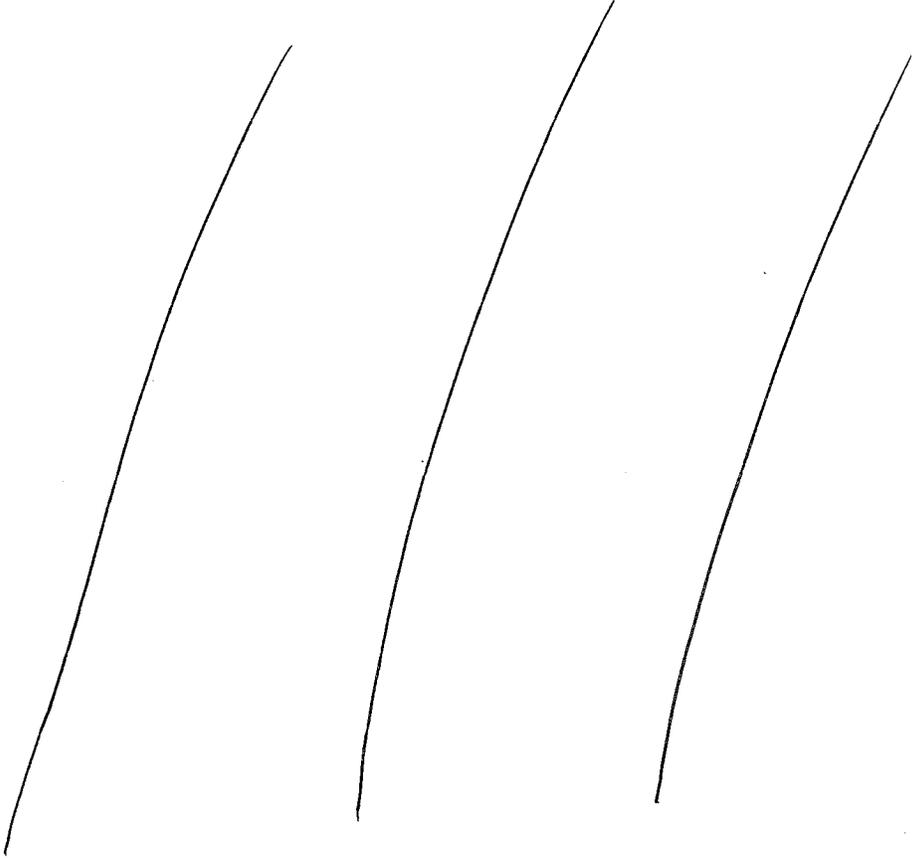
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NDA 21-254

We are reviewing your submission dated October 3, 2001, which contained clarifications to the _____ protocols as submitted June 29, 2001.



If you have any questions, please contact me at 301-827-5584.

Ladan Jafari, Regulatory Project Manager

NDA 21-254

Page 2

cc:

HFD-570/Div.files

HFD-570/Schroeder

HFD-570/Poochikian

Initialed by: Barnes/10-14-01
Schroeder/10-16-01
Poochikian/10-16-01

Filename:AdvairHFAcomments

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/s/

Ladan Jafari
10/16/01 04:01:24 PM
CSO

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: October 4, 2001

TO: Jafari, Laden, PM
Gilbert-McClain, Lydia I., M.D.
HFD-570

THROUGH: John Martin, M.D., Branch Chief
Good Clinical Practice Branch 1
Division of Scientific Investigations

FROM: H. W. Ju, M.D., GCP1, Reviewer

SUBJECT: Evaluation of Clinical Inspections

NDA: #21-254

APPLICANT: GlaxoSmithKline, Inc.

DRUG: ADVAIR™ HFA (fluticasone propionate/salmeterol inhalation Aerosol)

INDICATION: Treatment of asthma for adults and adolescents.

CONSULTATION REQUEST DATE: February 20, 2001

ACTION GOAL DATE: August 1, 2001

PDUFA DATE: October 1, 2001

I. BACKGROUND:

Goals of inspections are to verify the efficacy and safety endpoints generated by 4 studies.

The primary efficacy endpoints of the studies are FEV1 results (area under the serial FEV1 curve), mean change from baseline in AM pre-dose FEV1 at endpoint, and probability of remaining in the study

The safety endpoints are adverse events, clinical laboratory results, 12-lead ECGs, oropharyngeal exam, vital signs, and at selected sites, 24-hour Holster monitoring, short ACTH-stimulated plasma cortisol concentrations, and 24-hour urinary free cortisol.

Page 2 Advair Summary

II. RESULTS (by protocol/site):

NAME	CITY	STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION
		CA	06-MAR-01	13-JUN-01	VAI
		MA	06-MAR-01	25-MAY-01	NAI
		CA	06-MAR-01	11-MAY-01	NAI
		CT	06-MAR-01	18-JUN-01	VAI

II Protocols

A. Protocol #SAS30001

1. Site #15019 _____

There were no limitations to this inspection. There were 23 subjects enrolled into this study. Of the 23 subjects, 10 were screening failures, and 13 were randomized. Of the 13 randomized subjects, 11 completed the study. Two subjects dropped out of the study due to exacerbation of asthma. One of these two early withdrawals was classified as a Severe Adverse Event (SAE) since the subject was admitted to the hospital for close to a week. Adverse events and efficacy endpoints were verified against the Case Report Form Tabulations provided with the background material prior to the inspection. Due to an oversight, Dr. _____ neglected to send an amended protocol to the IRB for approval and nine subjects were enrolled into the study during the interim. However, this oversight did not affect the results of the study. The inspection covered a 100% review of informed consent forms for all subjects both screened and randomized into the study. Additionally, raw data were compared to data provided to CDER (line listings). No discrepancy was noted. A work sheet requested by the Reviewing Division Medical Officer (the values of the FEV1, potassium, and heart rate in the NDA) was compared against the original source data for 11 subjects. Only one subject #2561 heart rate from ECG was 77 (independent cardiologist reading) and the ECG tracing showed 81. The classification of this EIR is NAI. The data appear acceptable.

2. Site #25522 _____

There were no limitations to this inspection. Twelve subjects were enrolled and completed this study. All twelve subjects' records were reviewed. Record review consisted of verifying that the informed consent was available and signed prior to initiation of the study; that all adverse events documented were reported on the case report forms; and that all transcribed information was accurate (from the source document to the CRF and from the subject diary card to the CRF). In addition, record review verified that the protocol was followed as written and approved. The specific requests from the reviewing division are to verify the primary endpoints and confirm the presence of 100% signed and dated consent forms. These requests were performed along with comparing the values of FEV1, potassium and heart rate given in the NDA against the original data source. No discrepancy was observed. The classification of this EIR is NAI. The data appear acceptable.

B. Protocol #SAS30004

1. Site #24775 _____

There were no limitations to this inspection. Twenty-two subjects were enrolled and 16 subjects completed the study. All consent forms were reviewed. Certain minor deficiencies in the language of the consent forms were discussed with Dr. _____. However, these minor deficiencies were not entered on Form 483. A total of 11 subjects' files were reviewed in depth. In addition, files from various other subjects were reviewed in part with regard to specific questions. The raw data in the clinical investigator's records agreed with the case report files. All clinical laboratory testing, adverse reaction and listing of adverse events were supported with raw data documentation and reported in the subject's case report forms. As requested by the Reviewing Division MO, certain data points of 12 subjects for FEV1, K, and

Page 3 Advair Summary

heart rate from ECG submitted with the NDA were compared with source documents. No discrepancy was observed. Two items are cited in the form 483 as follows:

- a. Manufacturing records from _____, calibrating syringe, with serial #SY98050 used to calibrate the _____ spirometer testing system used throughout the study for pulmonary function testing, indicate that the unite (the calibration syringe) was originally calibrated when manufactured on 12/2/98. The manual for the _____ spirometer recommends that the syringe be re-calibrated annually. However, this re-calibration has never taken place;
- b. Patient #4077 had current cataracts during the visit 1 screening. However this subject was randomized to study drug despite the fact that the protocol lists historical or current cataracts as an exclusion. The sponsor was subsequently notified.

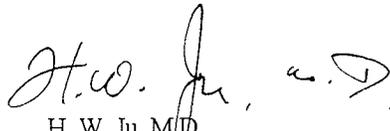
The classification of this EIR is VAI. The data appear acceptable.

2. Site #1369 _____

There were no limitations in this inspection. A total of 25 subjects were screened for the study, 19 of the 25 subjects were entered into the study and 14 of the 19 subjects completed the study. A comparison of the source documents in the clinical investigator's records with the electronic case report forms that were submitted by the sponsor found no discrepancies. All of the adverse experiences were documented in the clinic charts or in the subject diaries and documented in the electronic case report forms. Concomitant medications were also document. The end points (Potassium levels, heart rates from ECGs and FEV1 data) requested by the reviewing division were verifies and no discrepancies were observed. Although no Form 483 was issued, the protocol violations (three informed consent documents were missing from the file) were discussed with the PI. The classification of this EIR is VAI. The data appear acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Data generated by the four clinical investigators for the above 4 studies appear acceptable for consideration in the drug application. The results of this inspection were discussed with the reviewing Medical Officer at HFD-570. No follow-up actions are scheduled at this time.


H. W. Ju, M.D.
GCPBI Reviewer

CONCURRENCE:

Supervisory comments


John Martin, M.D. Chief
Good Clinical Practice Branch 1
Division of Scientific Investigations

Page 4 Advair Summary

DISTRIBUTION:

NDA 21-254

Division File

HFD-45/Program Management Staff (electronic copy)

HFD-46/GCP1/Prager

HFD-46/GCP1/Ju

HFD-46/GCP1/Martin

HFD-46/47/GCPB File #10373, #10392, #10364, #10396

HFD-46/47/Reading File

O:/ju/SummaryAdvair.doc

IND 53,502

NDA 21-254

Date of Telecon: August 22, 2001

Sponsor: GlaxoSmithKline

Sponsor representatives:

Paul Dorinsky, Clinical Development

Colin Reisner, Director, Clinical Development

Elaine Jones, Director, Regulatory Affairs

Michele Riebe, Director, New Product Supply

Satinder Sethi, Vice President, Inhaled Product Strategy

Susan Rider, Research Investigator, Inhalation Product Development

Alan Cripps, Head, MDI Development Projects, UK

Lorna Wilson, Director, Regulatory Affairs

Mary Sides, CMC Regulatory Affairs

Division of Pulmonary & Allergy Drug Products (DPADP)

Craig Bertha, CMC Reviewer

Ladan Jafari, Regulatory Project Manager

Robert Meyer, Director

Guirag Poochikian, CMC Team Leader

Brian Rogers, CMC Reviewer

Alan Schroeder, CMC Reviewer

Background: GlaxoSmithKline submitted a correspondence to the Division of Pulmonary & Allergy Drug Products (DPADP) on July 23, 2001, and requested that the Division provide comments regarding their proposed study protocol for the _____ study to be performed on Advair HFA NDA as well as the upcoming Flovent HFA NDA. The Division contacted GlaxoSmithKline on August 22, 2001, to discuss issues pertaining to the July 23, 2001, submission.

(m)

2 Page(s) Withheld

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Deliberative Process

IND 53,502
NDA 21-254
Date of the telecon: August 22, 2001
Sponsor: GlaxoSmithKline
Page 4

cc:

HFD-570/Divisionfiles
HFD-570/Bertha
HFD-570/Rogers
HFD-570/Schroeder
HFD-570/Poochikian
HFD-570/Jafari

Initialed by: Bertha/9-13-01
Rogers/9-13-01
Schroeder/9-13-01
Poochikian/9-15-01
Meyer/9-20-01

Filename: Patientmisuseprotocol

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this page is the manifestation of the electronic signature.**

/s/

Ladan Jafari
9/24/01 09:49:19 AM

Memorandum of Telephone Facsimile Correspondence

Date: August 14, 2001
To: Lorna Wilson
Regulatory Affairs
Fax: (919) 483-5381
From: Parinda Jani
Project Manager
Subject: NDAs 20-983 and 21-254/ Meeting dated June 8, 2001

Reference is made to the meeting held between representatives of your company and this Division on June 8, 2001. Attached is a copy of our final minutes for that meeting. These minutes will serve as the official record of the meeting. If you have any questions or comments regarding the minutes, please call me at (301) 827-1064.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 827-1050 and return it to us at FDA, 5600 Fishers Lane, HFD-570, DPDP, Rockville, MD 20857.

Thank you.

Meeting Date: June 8, 2001

Time: 10:00-11:30 AM

Location: Chesapeake Room

IMTS #: 6985

Sponsor: GlaxoSmithKline (GSK)

NDAs: 20-983 and 21-254

Products: Ventolin-HFA (albuterol sulfate inhalation aerosol)
ADVAIR-HFA (fluticasone propionate/salmeterol xinafoate inhalation aerosol)

Type of Meeting: CMC

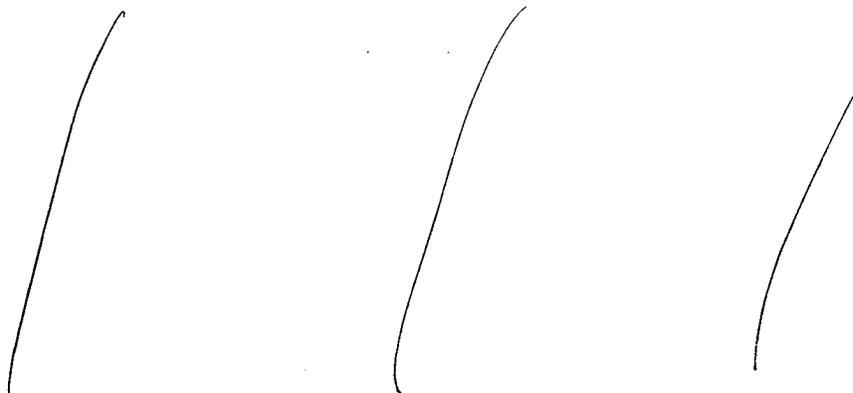
FDA Attendees:

Sandy Barnes	Chief, Project Management Staff
Craig Bertha, Ph.D.	Chemistry Reviewer
Parinda Jani	Project Manager
Robert Meyer, M.D.	Director, DPADP
Guirag Poochikian, Ph.D.	Chemistry Team Leader
Alan Schroeder, Ph.D.	Chemistry Reviewer

GSK Attendees:

Robert Bonura	Sr. Mgr., Production Engineer
Ramona Krailler, Ph.D.	Vice President, CMC Regulatory Affairs, and R & D Quality Assurance
Sue Rider, M.Sc.	Research Investigator, Inhalation Product Development
Stephen Plating	Vice president, Quality Assurance
Michael Riebe, Ph.D.	Director, New Product Strategy
Satinder Sethi, Ph.D.	Vice President, Inhaled Product Strategy
Lorna Wilson	Associate Director, Regulatory Affairs

Background: See the submission dated April 17, 2001. GSK requested this meeting to discuss the progress and some concerns regarding the _____ testing.



(10)

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/s/

Parinda Jani
8/17/01 11:27:43 AM



NDA 21-254

DISCIPLINE REVIEW LETTER

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

Attention: Lorna Wilson
Associate Director, Regulatory Affairs

Dear Ms. Wilson:

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

We also refer to your submissions dated February 9, 22, and 23, March 14, 15, 21, 26, and 30, April 17, and June 5 and 12, 2001.

Our review of the Chemistry, Manufacturing and controls section of your submission is complete, and we have identified the following deficiencies.

///

⑥

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19. Any comments regarding the status of supporting DMFs are deferred at this time.
20. CMC labeling comments are deferred at this time.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Mrs. Gretchen Trout, Project Manager, at (301) 827-1058.

Sincerely yours,

{See appended electronic signature page}

Guirag Poochikian, Ph.D.
Chemistry Team Leader
Division of Pulmonary and Allergy Drug Products HFD-570
DNDC 2, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Craig Bertha
8/13/01 11:04:31 AM
for G. Poochikian

Memorandum of Telephone Facsimile Correspondence

Date: May 7, 2001

To: Lorna Wilson
Regulatory Affairs

Fax: (919) 483-5381

From: Parinda Jani
Project Manager

Subject: NDA 21-254/ Meeting dated April 4, 2001

Reference is made to the meeting held between representatives of your company and this Division on April 4, 2001. Attached is a copy of our final minutes for that meeting. These minutes will serve as the official record of the meeting. If you have any questions or comments regarding the minutes, please call me at (301) 827-1064.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 827-1050 and return it to us at FDA, 5600 Fishers Lane, HFD-570, DPDP, Rockville, MD 20857.

Thank you.

Meeting Date: April 4, 2001

Time: 2:00-3.30 PM

Location: Conference Room 10B45

IMTS #: 6850

Sponsor: GlaxoSmithKline (GSK)

NDA: 21-254

Product: ADVAIR-HFA (fluticasone propionate/salmeterol xinafoate) Inhalation Aerosol

Type of Meeting: CMC

FDA Attendees:

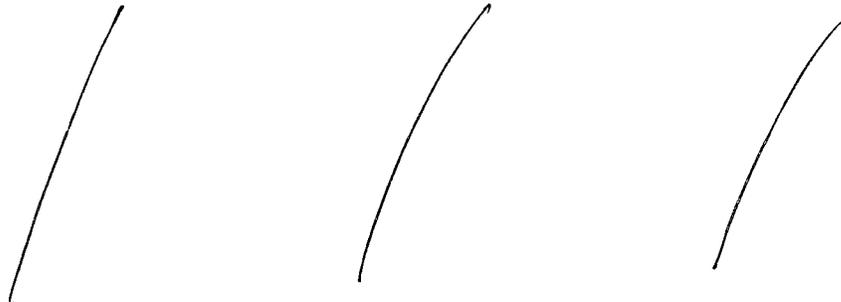
Craig Bertha, Ph.D.	Chemistry Reviewer
Parinda Jani	Project Manager
Marianne Mann, M.D.	Deputy Director, DPADP
Robert Meyer, M.D.	Director, DPADP
Guirag Poochikian, Ph.D.	Chemistry Team Leader
Alan Schroeder, Ph.D.	Chemistry Reviewer

Glaxo Attendees:

Robert Bonura	Sr. Mgr., Production Engineer
John Morgan, Ph.D.	Director, Regulatory Affairs
Sue Rider, M.Sc.	Research Investigator, Inhalation Product Development
Michael Riebe, Ph.D.	Director, New Product Strategy
Satinder Sethi, Ph.D.	Vice President, Inhaled Product Strategy
Lorna Wilson	Associate Director, Regulatory Affairs

Background: Preliminary CMC comments were provided to GSK on March 12, 2001. The purpose of providing these comments was to give GSK advance notification of certain critical issues for which additional data might be required and/or issues that need to be resolved before approval of this NDA. GSK provided response to these comments in their March 21, 2001, submission. This meeting was scheduled to provide further clarification.

At the beginning of the meeting, the Division made it clear that the comments sent to GSK were not generated from full review of the application. They were preliminary comments about issues that may have impact on timely approval of this application. The purpose of the meeting is just to provide clarification, not to accept/reject any proposals made in response to the comments.



(P)

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/s/

Parinda Jani
5/7/01 02:57:52 PM

Memorandum of Telephone Facsimile Correspondence

Date: March 7, 2001

To: Joy Farrell
Regulatory Affairs

From: Parinda Jani
Project Manager

Subject: Comments NDA 21-254

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 827-1050 and return it to us at FDA, 5600 Fishers Lane, HFD-570, DPDP, Rockville, MD 20857.

Thank you.

On page 74 of volume 8.1 it said there were 25 patients on placebo who withdrew for lack of efficacy (worsening asthma). On page 85 of that volume, it said there were only 24 patients on placebo that withdrew for worsening asthma. The last analysis was one of the primary endpoints.

On page 73 of volume 8.4 it said there were 23 patients on SALM 42 and 11 on FP 220 who withdrew for worsening asthma. On page 81 of that volume, it said there were 22 patients on SALM 42 and 10 patient on FP 220. The last analysis was one of the primary endpoints.

Please explain these differences and specify the patients involved in the discrepancies.

Study SFCB3023

There were 6 patients (3 on SFC 440/42 MDI, 2 on SFC 500/50 Diskus, and 1 on FP 440 MDI) who were not included in the primary efficacy analysis. The primary efficacy analysis included 503 patients (173 on SFC 440/42 MDI, 159 on SFC 500/50 Diskus and 171 on FP 440 MDI).

Explain the reasons that these six patients were not included.

/s/

Parinda Jani

3/9/01 03:24:28 PM

CSO

GlaxoWellcome

December 8, 2000

Mellon Bank
Food and Drug Administration
27th Floor (FDA 360909)
Three Mellon Bank Center
Pittsburgh, PA 15259-0001

**Re: NDA 21-254; ADVAIR™ HFA (fluticasone propionate/salmeterol xinafoate) Inhalation
Aerosol 44mcg/21mcg, 110mcg/21mcg, 220mcg/21mcg
User Fee: With Clinical Data
User Fee # 4059**

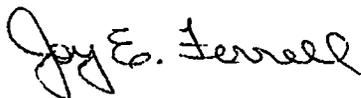
Please find enclosed Glaxo Wellcome check number 1736923 in the amount of \$285,740.00. This payment is 100% of the application fee for the New Drug Application: Maintenance Treatment of Asthma in Patients 12 Years of Age and Older. This application will be submitted to the Division of Pulmonary and Allergy Drug Products, Center for Drug Evaluation and Research, FDA.

Please find below requested information regarding this application.

Type of Application:	New Drug Application with Clinical Data	X
	New Drug Application without Clinical Data	
	Supplemental new Drug Application with Clinical Data	

Should you have any questions, please contact E. Allen Jones at (919) 483-9122.

Sincerely,



Joy E. Ferrell
Director
Regulatory Affairs

Glaxo Wellcome Inc.

Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709-3398

Telephone
919 483 2100

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form.

<p>1. APPLICANT'S NAME AND ADDRESS</p> <p>Glaxo Wellcome Inc. Five Moore Drive Research Triangle Park, NC 27709</p>	<p>3. PRODUCT NAME</p> <p>ADVAIR HFA (fluticasone propionate/salmeterol xinafoate) Inhalation Aerosol, 44mcg/21mcg, 110mcg/21mcg, 220mcg/21mcg</p> <p>4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? Yes IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.</p> <p>IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:</p> <p><input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.</p> <p><input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).</p>
<p>2. TELEPHONE NUMBER (Include Area Code)</p> <p>(919) 483-2100</p>	<p>6. LICENSE NUMBER / NDA NUMBER</p> <p>NDA 21-254</p>

<p>5. USER FEE I.D. NUMBER</p> <p>4059</p>	<p>6. LICENSE NUMBER / NDA NUMBER</p> <p>NDA 21-254</p>
---	--

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE. (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, drug, and Cosmetic Act (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)	

FOR BIOLOGICAL PRODUCTS ONLY

<input type="checkbox"/> WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION	<input type="checkbox"/> A CRUDE ALLERGENIC EXTRACT PRODUCT
<input type="checkbox"/> AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY	<input type="checkbox"/> AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT
<input type="checkbox"/> BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92	

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO (See reverse side if answered YES)

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

<p>SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE</p> <p><i>Joy E. Ferrell</i> Joy E. Ferrell</p>	<p>TITLE</p> <p>Director, Regulatory Affairs</p>	<p>DATE</p> <p>December 8, 2000</p>
---	---	--

FOOD AND DRUG ADMINISTRATION
P.O. BOX 360909
PITTSBURGH PA 15259-0001

GlaxoWellcome

P.O. BOX 13358
RESEARCH TRIANGLE PARK, N.C. 27709

DATE
11/15/00
RTPT

CHECK NO.
1736923
010340 PA

DATE	INVOICE/CREDIT MEMO	TYPE	DESCRIPTION	GROSS	DISCOUNT	NET
11/01/00	GLAXO INTERNAL USE ONLY: GUNNELL, NDA21254 ALLEN JONES 5.5546		WINTER	285740.00	STH D2644 00	483-910 285740.00
				285740.00	0.00	285740.00
TOTAL						

VERIFY THE AUTHENTICITY OF THIS MULTI-TONE SECURITY DOCUMENT. CHECK BACKGROUND AREA CHANGES COLOR GRADUALLY FROM TOP TO BOTTOM.

GlaxoWellcome

P.O. BOX 13358
RESEARCH TRIANGLE PARK, N.C. 27709

Wachovia Bank & Trust Company, N.A.
Winston-Salem

66-35
531

CHECK DATE
11/15/2000

CHECK NUMBER
1736923

CHECK VOID AFTER 120 DAYS

PAY ONLY 285740.00

***\$285,740.00

TWO HUNDRED EIGHTY-FIVE THOUSAND SEVEN HUNDRED FORTY DOLLARS AND 00 CENTS *****

Pay to the order of
FOOD AND DRUG ADMINISTRATION
P.O. BOX 360909
PITTSBURGH PA 15259-0001

Michael A. Galt

Authorized Signature

⑈ 1736923⑈ ⑆053107633⑆010459 002194⑈