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

FACSIMILE TRANSMITTAL SHEET

DATE: January 16, 2007

To: Michael Golden	**From:** Ladan Jafari
Company: GSK	Division of Pulmonary and Allergy Products
Fax number: 919-483-5381	**Fax number:** 301-796-9728
Phone number: 919-483-3692	**Phone number:** 301-796-1231

Subject: NDA 22-051

Total Number of Pages Including Cover: 3

Comments: CMC comments

Document to be mailed: ☐ YES ☑ NO

NDA 22-051

Dear Dr. Abdullah:

We are reviewing your NDA for fluticasone furoate nasal spray, and we have the following requests for information. We ask that you respond to these requests by COB on January 26, 2007.

1. Provide the following for the Zero Tolerance methods:

   a. Specify the sample sizes used in each test.

   b. For the Delivered Dose Uniformity measurement, clarify if each determination (at all time points) is a single spray or a mean of two sprays.

   c. Update the specifications table for the Spray Weight Uniformity, Delivered Dose Uniformity and Droplet Size Distribution to include target values and express the range as a percentage of the target value (e.g., 85-115% of proposed target).

   d. For the Droplet Size Distribution method, clarify why you have defined the Standard Deviation for the means and individuals differently. Clarify how you would distinguish between the mean D10 and individual D10 values.

   e. Give an example to illustrate the computations for the mean and individual determinations for Spray weight uniformity, Delivered Dose Uniformity and Droplet Size Distribution.

   f. Provide the data used to generate the OC curves for these methods.

2. Provide the following information for the PTI Testing method for Delivered Dose Uniformity testing:

   a. Clarify if each determination is a mean of two sprays. Each determination should be considered as one spray. Refer to the Agency proposal for PITI Testing.

   b. Clarify why the mean of beginning values and the mean of end values were deleted.

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

Ladan Jafari, Regulatory Health Project Manager

NDA 22-051

Drafted by: LJ/1-12-07

Initialed by: Tsong/1-12-07
Shen/1-12-07
Nashed/1-12-07
Peri/1-12-07
Fraser/1-12-07

Filename: N22051CMCIR2

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/s/

Ladan Jafari
1/16/2007 09:26:57 AM
CSO

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

FACSIMILE TRANSMITTAL SHEET

DATE: December 21, 2006

To: Munir Abdullah	**From:** Ladan Jafari
Company: GSK	Division of Pulmonary and Allergy Products
Fax number: 919-315-0033	**Fax number:** 301-796-9728
Phone number: 919-483-9318	**Phone number:** 301-796-1231

Subject: NDA 22-051

Total Number of Pages Including Cover: 7

Comments: CMC comments

Document to be mailed: ☐ YES ☑ NO

Dear Dr. Abdullah:

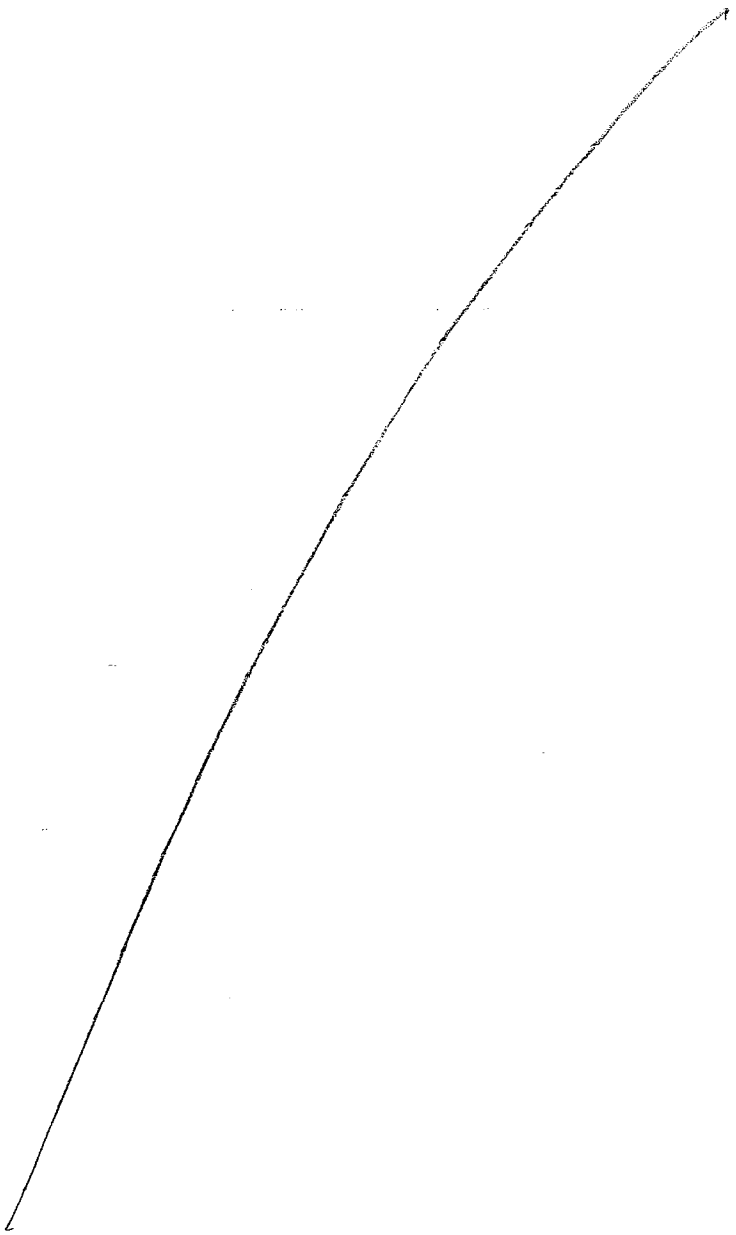
We are reviewing your NDA for fluicasone furoate nasal spray submitted on June 28, 2006. We have the following comments and requests for information. We request that you submit your response by close of business on January 26, 2007.

1. The following comments pertain to drug substance manufacturing and controls.

a.

b.

c.



3 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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

_____
Ladan Jafari, Regulatory Health Project Manager

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/s/

Ladan Jafari
12/21/2006 02:35:01 PM
CSO

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Dr. Wiley Chambers
vision of Anti-Infective and Opthamic Products

FROM *(Name, Office/Division, and Phone Number of Requestor)*:
Ladan Jafari, RPM, Division of Pulmonary and Allergy Products 301-796-1231

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
December 8, 2006		22-051	New NDA	June 28, 2006

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
fluticasone furoate nasal spray	S	Respiratory	January 19, 2007

NAME OF FIRM: GlaxoSmithKline

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- OTHER (SPECIFY BELOW):

- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: We are evaluating another NDA for a nasal steroid, fluticasone furoate, indicated for allergic rhinnitis. This steroid is very lipophilic and appears quite potent when administered topically. In addition to alleviating nasal allergic symptoms, it also reduces eye symptoms when administered intranasally. In a year-long safety study conducted with the proposed dose of the drug, we are concerned that a potential signal for cataract development may exist; 1 placebo subject developed a cataract during the study while 6 receiving the fluticasone developed cataracts. Although not all cataracts were posterior subcapsular in nature, we would appreciate it if someone with more "eye" experience could look at the data. This is an all electonic NDA (# 22051) . It is study FF102123. Here is the EDR link <<\\Cdsesub1\n22051\N_000\2006-06-28\clinstat>>.

IATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Ladan Jafari	☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Ladan Jafari
12/11/2006 08:32:28 AM

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

FACSIMILE TRANSMITTAL SHEET

DATE: December 6, 2006

To: Munir Abdullah	**From:** Ladan Jafari
Company: GSK	Division of Pulmonary and Allergy Products
Fax number: 919-315-0033	**Fax number:** 301-796-9728
Phone number: 919-483-9318	**Phone number:** 301-796-1231

Subject: NDA 22-051

Total Number of Pages Including Cover: 3

Comments: CMC comments

Document to be mailed: ☐ YES ☑ NO

Dear Dr. Abdullah:

We are reviewing your NDA submission for fluticasone furoate nasal spray and we have the following requests for information. We ask that you provide the response by close of business on December 12, 2006.

1. Provide the following information for each of the three alternative Quality Assurance tests (Spray Weight Uniformity, Spray Content Uniformity and Droplet Size Distribution), to be performed by PTIT approach:

   a. Operating characteristic (OC) curves (the acceptance probability against the lot standard deviation) for the conventional approach (zero tolerance) for each of the two stages and the overall stage.

   b. OC curves (the acceptance probability against the lot standard deviation) for the proposed alternative PTIT approach for each of the two stages and the overall stage.

   c. Overlay plots for each of the two approaches for each stage and the overall stage.

   d. Modify the PTIT approach specification to control the probability below the lower limit and the probability above the upper limit separately (two one sided tests),

   e. The target values for the D_{10}, D_{50}, D_{90} and the mean for the Droplet Size Distribution specifications.

   f. The target value for the Spray Weight.

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

_____

Ladan Jafari, Regulatory Health Project Manager

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/s/

Ladan Jafari
12/6/2006 10:36:48 AM
CSO

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

FACSIMILE TRANSMITTAL SHEET

DATE: December 4, 2006

To: Munir Abdullah	**From:** Ladan Jafari
Company: GSK	Division of Pulmonary and Allergy Products
Fax number: 919-315-0033	**Fax number:** 301-796-9728
Phone number: 919-483-9318	**Phone number:** 301-796-1231

Subject: NDA 22-051

Total Number of Pages Including Cover: 7

Comments: Tradename comments

Document to be mailed: ☐ YES ☑ NO

5 Page(s) Withheld

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_____ § 552(b)(5) Deliberative Process

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/s/

Ladan Jafari
12/4/2006 09:15:01 AM
CSO

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*: IRT for QT studies

FROM *(Name, Office/Division, and Phone Number of Requestor)*: Ladan Jafari, Regulatory Health Project Manager, Division of Pulmonary and Allergy Products 301-796-1231

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
February 5, 2007		22-051	Safety Update Report	October 18, 2006

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
fluticasone furoate nasal spray	S	Respiratory	March 20, 2007

NAME OF FIRM: GlaxoSmithKline

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Please review the QT data contained in study FFR101888. This information is available in the EDR dated October 18, 2006.

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Ladan Jafari	☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Ladan Jafari
2/5/2007 09:56:22 AM

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Pharmacology and Toxicology Team, DPADP

ing Hao, Ph.D. / Timothy McGovern, Ph.D.

FROM *(Name, Office/Division, and Phone Number of Requestor)*:
Eugenia Nashed, Office of New Drug Quality Assessment, Division 1, Branch 2, 301-796-1723

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
November 27, 2006		22-051	New NDA	June 28, 2006

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
fluticasone furoate nasal spray	S	Respiratory	February 9, 2006

NAME OF FIRM: GlaxoSmithKline

REASON FOR REQUEST I. GENERAL

NEW PROTOCOL PROGRESS REPORT NEW CORRESPONDENCE DRUG ADVERTISING ADVERSE REACTION REPORT MANUFACTURING CHANGE / ADDITION MEETING PLANNED BY PRE-NDA MEETING END-OF-PHASE 2a MEETING END-OF-PHASE 2 MEETING RESUBMISSION SAFETY / EFFICACY PAPER NDA CONTROL SUPPLEMENT RESPONSE TO DEFICIENCY LETTER FINAL PRINTED LABELING LABELING REVISION ORIGINAL NEW CORRESPONDENCE FORMULATIVE REVIEW OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

RITY P NDA REVIEW END-OF-PHASE 2 MEETING CONTROLLED IES PROTOCOL REVIEW OTHER (SPECIFY BELOW):	CHEMISTRY REVIEW PHARMACOLOGY BIOPHARMACEUTICS OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

DISSOLUTION BIOAVAILABILTY STUDIES PHASE 4 STUDIES DEFICIENCY LETTER RESPONSE PROTOCOL - BIOPHARMACEUTICS IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES CASE REPORTS OF SPECIFIC REACTIONS (List below) COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY SUMMARY OF ADVERSE EXPERIENCE POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL	NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Please evaluate the safety of the proposed specifications for drug substance impurities and observed levels of leachables in the drug product. This NDA is fully electronic and the NDA is dated June 28, 2006, and the information you need can be found in section 3.2.S.4.1 (Specification), 3.2.S.4.5 (Justification), and 3.2.P.2, pp. 154-157 (Leachables).

SIGNATURE OF REQUESTOR Eugenia Nashed, Ph.D.	METHOD OF DELIVERY (Check one) DFS EMAIL MAIL HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Eugenia Nashed
11/27/2006 07:21:42 PM

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

FACSIMILE TRANSMITTAL SHEET

DATE: November 17, 2006

To: Munir Abdullah	**From:** Ladan Jafari
Company: GSK	Division of Pulmonary and Allergy Products
Fax number: 919-315-0033	**Fax number:** 301-796-9728
Phone number: 919-315-9318	**Phone number:** 301-796-1231

Subject: NDA 22-051

Total Number of Pages Including Cover: 3

Comments: Stat comments

Document to be mailed: ☐ YES ☑ NO

NDA 22-051

Dear Dr. Abdullah:

We are reviewing your NDA for fluticasone furoate nasal spray and we would like to discuss the following observations at the teleconference scheduled for Monday November 20.

Attached you will find the printout of data from 3 patients that illustrate some problems found in the data recorded in dataset RQLQ ANL.xpt and RQLQ.xpt. Attached you will also find the description of the scoring of RQLQ from the RAP.

Note that for patients 10 and 17, data are available at baseline and endpoint for the activities domain (dataset RQLQ.xpt), however, the average of the endpoint scores is missing in dataset RQLQ ANL.xpt.

It appears that if the description of the activity is precisely the same for both baseline and endpoint (as for patient 1 on the attached printout), the averages are correct.

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

_____

Ladan Jafari, Regulatory Health Project Manager

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/s/

Ladan Jafari
11/17/2006 01:37:43 PM
CSO

September 29, 2006

GlaxoSmithKline

Badrul A. Chowdhury, M.D., Director
Division of Pulmonary and Allergy Products
Food and Drug Administration
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

GlaxoSmithKline
PO Box 13398
Five Moore Drive
Research Triangle Park
North Carolina 27709
Tel. 919 483 2100
www.gsk.com

Re: NDA 22-051; Fluticasone Furoate Nasal Spray
General Correspondence: Other; Statement of Claimed Exclusivity

Dear Dr. Chowdhury:

Reference is made to the above referenced NDA for Fluticasone Furoate Nasal Spray submitted on June 28, 2006 and to FDA letter dated September 1, 2006 notifying that the NDA has been filed under section 505(b) of the Federal Food, Drug and Cosmetic Act. As stated in Module 1.3.5.3 of NDA 22-051, we have now provided under a separate cover the enclosed information on "Statement of Claimed Exclusivity for Fluticasone Furoate Nasal Spray" to Sheldon T. Bradshaw, Esq., Chief Counsel, FDA, with copies provided to yourself, Elizabeth H. Dickinson, Esq., Dr. John Jenkins, and Dr. Robert Temple. In this submission we are providing the information sent to Sheldon T. Bradshaw, Esq. for the NDA files.

This submission is provided in electronic format. Please see the attached Guide to Reviewer for complete details regarding this electronic submission. If you have any questions regarding this submission, please contact me at (919) 483-9318.

Sincerely,

Munir Abdullah

Munir Abdullah, Ph.D.
Director
Regulatory Affairs

Trade secret and/or confidential commercial information contained in this submission is exempt from public disclosure to the full extent provided under law.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 48,647

INFORMATION REQUEST LETTER

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

Attention: Munir Abdullah, Ph.D.
Director, Regulatory Affairs

Dear Dr. Abdullah:

Please refer to your June 28, 2006, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for fluticasone furoate nasal spray.

We also refer to your submission to IND 48,647 dated December 5, 2005, which was to propose "———" as the tradename for this new drug application. We completed the review of this submission and have the following comments.

We object to the proposed tradename "———" because it has the potential of medication error with other approved drug products. We request a prompt written response in order to continue our evaluation of your application.

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

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury. M.D., Ph.D.
Director
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Badrul Chowdhury
11/16/2006 10:12:54 AM

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Division of Biometrics, Karl Lin, Ph.D.			FROM *(Name, Office/Division, and Phone Number of Requestor)*: Ladan Jafari, Division of Pulmonary and Allergy Products, 301-796-1231	
DATE September 19, 2006	IND NO.	NDA NO. 22-051	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT June 28, 2006
NAME OF DRUG fluticasone furoate nasal spray	PRIORITY CONSIDERATION S		CLASSIFICATION OF DRUG Respiratory	DESIRED COMPLETION DATE November 17, 2006

NAME OF FIRM: GlaxoSmithKline

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☒ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Please evaluate the tumor incidences in rats and mice. This NDA is fully electronic and the NDA is dated June 28, 2006, and the information you need can be found in the carcinogenicity studies for rats and mice.

SIGNATURE OF REQUESTOR Ladan Jafari	METHOD OF DELIVERY (Check one) ☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Ladan Jafari
9/21/2006 11:10:08 AM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-051 Supplement # Efficacy Supplement Type SE-

Proprietary Name: fluticasone furoate nasal spray
Established Name:
Strengths: —.ncg/actuation

Applicant: GSK
Agent for Applicant (if applicable):

Date of Application: June 28, 2006
Date of Receipt: June 29, 2006
Date clock started after UN:
Date of Filing Meeting: August 22, 2006
Filing Date: August 28, 2006
Action Goal Date (optional): User Fee Goal Date: April 29, 2006

Indication(s) requested: Seasonal and perennial allergic rhinitis

Type of Original NDA:	(b)(1) x	(b)(2) ☐
AND (if applicable)		
Type of Supplement:	(b)(1) ☐	(b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S x P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 2
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES x NO ☐

User Fee Status: Paid x Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES x NO ☐
  If yes, explain: The active moiety (fluticasone) is subject of a few other NDAs such as Flovent HFA, and Advair HFA.

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO x

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO x
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES x NO ☐
  If no, explain:

- Was form 356h included with an authorized signature? YES x NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES x NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐

2. This application is an eNDA or combined paper + eNDA YES X
   This application is: All electronic x Combined paper + eNDA ☐
   This application is in: NDA format ☐ CTD format ☐
   Combined NDA and CTD formats ☐

   Does the eNDA, follow the guidance?
   (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES x NO ☐

   If an eNDA, all forms and certifications must be in paper and require a signature.

   If combined paper + eNDA, which parts of the application were submitted in electronic format?

   Additional comments:

3. This application is an eCTD NDA. YES ☐
   If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES x NO ☐
- Exclusivity requested? YES, 5 Years NO ☐
  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*
- Correctly worded Debarment Certification included with authorized signature? YES x NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] 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." Applicant may not use wording such as "To the best of my knowledge . . . ."*
- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
  YES x NO ☐
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☐ NO ☐
- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO X

  If yes, contact PMHT in the OND-IO
- Financial Disclosure forms included with authorized signature? YES x NO ☐
  (Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*
- Field Copy Certification (that it is a true copy of the CMC technical section) YES x NO ☐
- PDUFA and Action Goal dates correct in tracking system? YES x NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: 48,647and 70,297
- Are the trade, established/proper, and applicant names correct in COMIS? YES x NO ☐
  If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) July 19, 2004 NO ☐
  If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) CMC: January 20, 2006, other disciplines: February 13, 2006 NO ☐

If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO X
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES x NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES X NO

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES X NO ☐

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES X NO ☐

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☐ YES X NO ☐

- Risk Management Plan consulted to OSE/IO? N/A X YES ☐ NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA X YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES X NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to EA officer, OPS? YES ☐ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES X NO ☐

- If a parenteral product, consulted to Microbiology Team? YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 22, 2006

NDA #: 22-051

DRUG NAMES: fluticasone furoate nasal spray

APPLICANT: GSK

BACKGROUND: GSK submitted this new NDA for fluticasone furoate nasal spray for SAR and PAR. This formulation is a new ester of the previously approved fluticasone that is subject of a few NDAs, such as Flovent and Advair.
(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Anthony Durmowicz, Sally Seymour, Badrul Chowdhury, Sayed Al-Habet, Emmanuel Fadiran, Prasad Peri, Huiqing Hao, Timothy McGovern, Feng Zhou, Ruthie Davi, Ladan Jafari

ASSIGNED REVIEWERS (including those not present at filing meeting) : Anthony Durmowicz, Eugenia Nashed, Sayed Al-Habet, Feng Zhou, Huiqing Hao,

Discipline/Organization	Reviewer
Medical:	Anthony Durmowicz, M.D
Secondary Medical:	Sally Seymour, M.D
Statistical:	Feng Zhou, M.S
Pharmacology:	Huiqing Hao, Ph.D.
Statistical Pharmacology:	N/A
Chemistry:	Eugenia Nashed, Ph.D.
Environmental Assessment (if needed):	
Biopharmaceutical:	Sayed Al-Habet, Ph.D.
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	
DSI:	
OPS:	
Regulatory Project Management:	Ladan Jafari
Other Consults:	

Per reviewers, are all parts in English or English translation? YES X NO ☐
If no, explain:

CLINICAL FILE X REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☐ NO X

If no, explain: No evidence of treatment by site interaction. Molecular entity is approved for SAR and PAR. Those investigators who had a significant interest in the application, enrolled relatively few subjects in the trials.

- Advisory Committee Meeting needed? YES, date if known _____ NO X

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A X YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A X FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE X REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE X REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? ☐ NO X
  YES

PHARMACOLOGY/TOX N/A ☐ FILE X REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO X

CHEMISTRY FILE X REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES X NO ☐
- Sterile product? YES X NO
  If yes, was microbiology consulted for validation of sterilization? YES X NO ☐

ELECTRONIC SUBMISSION:
Any comments: None

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

X The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

☐ No filing issues have been identified.

X Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☐ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. ☐ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5. ☐ Convey document filing issues/no filing issues to applicant by Day 74.

Ladan Jafari
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☐

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)
YES ☐ NO ☐

If "Yes," skip to question 7.

4. Is this application for a recombinant or biologically-derived product?
YES ☐ NO ☐

If "Yes "contact your ODE's Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?
   YES ☐ NO ☐

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," to (a) skip to question 6. Otherwise, answer part (b and (c)).

   (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

   (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐

If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.
Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☐

(***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," to (a) skip to question 7. Otherwise, answer part (b and (c)).

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes**," to (c), proceed to question 7.*

***NOTE:** If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**No**," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.*

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES ☐ NO ☐

If "No," skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☐

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☐

11. Is the application for a duplicate of a listed drug whose only difference is YES ☐ NO ☐

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES ☐ NO ☐

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ Not applicable (e.g., solely based on published literature. See question # 7

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES ☐ NO ☐

*If "**Yes**," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug*
Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A ☐ YES ☐ NO ☐

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES ☐ NO ☐

If "**Yes**," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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
9/8/2006 07:41:45 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-051

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

Attention: Munir Abdullah, Ph.D.
Director, Regulatory Affairs

Dear Dr. Abdullah:

Please refer to your June 28, 2006, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for fluticasone furoate nasal spray.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on August 28, 2006, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

Previously identified issues related to the lack of an identified no observed adverse effect level (NOAEL) for the finding of bile tract epithelial vacuolation in dogs are currently unresolved. We note that you are conducting a reevaluation of the tissue samples via a pathology panel scheduled for September 2006. We will revisit this issue once the conclusions of the pathology panel are submitted.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

1. Provide full-size mock ups of the carton and container labels.

2. For ease of review and assessing trends, provide stability data in a graphical form for each parameter. Include the time in months on the x-axis and the results (individual and mean) on the y-axis indicating the proposed acceptance criteria for each parameter. Provide the currently available stability data in the graphical format under all conditions and orientations tested for all relevant batches. If such a data presentation has already been provided, please provide a reference to the document and page number.

3. Submit the final study report for the in vivo micronucleus assay in rats at intravenous doses up to 40 mg/kg. We request that you submit this report by December 15, 2006.

4. The following comments pertain to the labeling that was submitted according to the Physician Labeling Rule format.

    a. The drug names must be followed by the drug's dosage form and route of administration. Do not include the dose (i.e., 27.5 mcg). [See 21 CFR 201.57(a)(2)]

    b. When the labeling is in final draft, the Highlights must be limited in length to one half page, in 8 point type. [See 21 CFR 201.57(d)(8)]

    c. The Agency recommends the use of a two-column format for the Highlights and Full Prescribing Information: Contents. [Implementation Guidance]

    d. We note that Structured Product Labeling (SPL) has been submitted; however, it appears technically inadequate for review. Please contact spl@fda.hhs.gov if you require further assistance.

    e. Please submit the completed Highlights Data Elements Table. To complete the Highlights data elements, please refer to the following two documents at the FDA Data Standards Council website (http://www.fda.gov/oc/datacouncil) under SPL:

        (1) "Companion Document for SPL Release 2 Implementation Guide for Highlights DRAFT" and "SPL Highlights Data Element Table." This table must be filled out with the terms that have been proposed for the Highlights data elements. The companion document provides information on the terminology to be used. If you need assistance completing the Highlights data elements portion of your application, please contact spl@fda.hhs.gov.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

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

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Badrul Chowdhury
9/1/2006 09:41:56 AM

-DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		**REQUEST FOR CONSULTATION**	
TO *(Division/Office)*: Division Microbial Review Team (Drs. David Hussong and Jim McVey)/OPS		FROM: Prasad Peri, Ph.D. PAL for DPAP in ONDQA/DPA1/Branch 2	
DATE Aug. 29, 2006	NDA. 22-051	TYPE OF DOCUMENT: Original NDA	DATE OF DOCUMENT June 28, 2006
NAME OF DRUG Fluticasone Furoate Nasal Spray	PRIORITY CONSIDERATION: S	CLASSIFICATION OF DRUG: 1	DESIRED COMPLETION DATE Nov 1st, 2006
NAME OF FIRM: Dey LP			
REASON FOR REQUEST: Evaluation of **Microbial Assurance in the Drug Product,** **Suitability of the Microbial Limit Tests (Rapid Microbial Test and Conventional Microbial Test)**			
COMMENTS/SPECIAL INSTRUCTIONS: A rationale for using the rapid microbial test is provided in the Pharmaceutical Development section (3.2.P.2) of this electronic NDA. The proposed specifications for the drug product are provided in the following pages. Microbial limits are not proposed for the drug substance.			

MEMORANDUM

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

DATE: August 29, 2006

FROM: Prasad Peri, Ph.D.

SUBJECT: Consult Request

THRU: Dr. Blair Fraser, Branch Chief, Branch II, ONDQA

TO: Dr. Stella Machado/ Drs. Yi Tsong and Meiyu Shen
Supervisor, Math Stat., OPSS/OB/QMRS

This is a formal consult request to evaluate the alternate acceptance criteria based on Parametric Tolerance Interval Tests. This approach has been proposed for controlling

Spray Weight Uniformity,
Spray Content Uniformity and
Droplet Size Distribution

in **NDA 22-051 (Fluticasone Furoate Nasal Spray) submitted July 28, 2006**. Details of the methods are provided in the electronic document room file in the CMC section 3.2.P.5.6. **Justification of Specifications**, under "Alternative Acceptance Criteria Based on Parametric Tolerance Interval Tests". In particular I would also appreciate if you could comment on the PTIT acceptance criteria and how they would compare to the zero tolerance approach which is also proposed.

For ease of review, I have summarized them in this consult. **I would like to request that you respond to this consult request by the end of Nov. 29, 2006.**

cc:	Orig. NDA#22051 HFD-570/Division File HFD-570/ENashed HFD-570/BFraser HFD-570/LJafari	R/D init. by: F/T by: Prasad Peri/ file:

ALTERNATIVE ACCEPTANCE CRITERIA BASED ON PARAMETRIC TOLERANCE INTERVAL TESTS

Alternative acceptance criteria derived from Parametric Tolerance Interval Tests (PTIT) are also provided for key measures of device performance, where

$$L = |100 - \text{Overall Mean}| + k * \text{Overall Standard Deviation}$$

where the Overall Mean and Standard Deviations are expressed as % of Target

Each ex-device test is initially performed on 10 devices and yields 20 results. In the event that second tier testing is necessary, an additional 20 devices are sampled to give 60 results in total. Values for the coefficient k are provided in Table 4 for 87.5% and 90.0% coverage and first and second tier sample sizes of 20 and 60 results.

Table 4 Coefficient Values

Coverage	k	
	First Tier Testing	Second Tier Testing
	n=20	n=60
87.5%	—	—
90.0%	—	—

Proposals are presented below for target intervals (L) and coverage for Pump Spray Weight, Spray Content Uniformity and D_{10}, D_{50} and D_{90} parameters of the Droplet Size Distribution.

3.1. Spray Weight Uniformity

A Parametric Tolerance Interval Test with a target interval of — (L = 20) with 90% coverage would assure that at least 90% of sprays delivered from a batch of Fluticasone Furoate Nasal Spray are in the range — mg. Additionally, the mean results from both the beginning and the end of the 10 or 30 devices must fall within the range — of target. These acceptance criteria are consistent with the Agency's proposal of October 4, 2005.

3.2. Spray Content Uniformity

A Parametric Tolerance Interval Test with a target interval of — (L = 20) with 87.5% coverage would assure that at least 87.5% of sprays delivered from a batch of

2 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Blair Fraser
8/30/2006 02:41:07 PM

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**22-051**	**Brand Name**	**N/A**
OCP (I, II, III)	**II**	**Generic Name**	**Fluticasone Furoate**
Medical Division	**DPADP**	**Drug Class**	Glucocorticoid
OCPB Reviewer	Sayed (Sam) Al Habet, RP.h, Ph.D.	**Indication(s)**	Seasonal and Perennial Rhinitis
OCPB Team Leader	**Emmanuel (Tayo) Fadiran, RP.h., Ph.D.**	**Dosage Form**	**Nasal Spray**
PM Reviewer		**Dosing Regimen**	**2 sprays (110 mcg) per nostril daily. Maintenance dose: 55 mcg QD one spray per nostril.**
Date of Submission	**June 28, 2006**	**Route of Administration**	**Nasal**
Estimated Due Date of OCP Review	**January 28, 2007**	**Sponsor**	**GSK**
PDUFA Due Date	**April 29, 2007**	**Priority Classification**	Standard
Division's Due Date	February 28, 2007		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	8		
multiple dose:	x	6		
Patients-				
single dose:	x	2		
multiple dose:		4		
Dose proportionality -				
fasting / non-fasting single dose:	x	2		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				

In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:	x	6		
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	x	7		
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		48		

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	Reasons if the application <u>is not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?	**No Comments at this time.**	Comments have been sent to firm (or attachment included). FDA letter date if applicable. NONE at this time
QBR questions (key issues to be considered)		

Other comments or information not included above	
Primary reviewer Signature and Date	
Secondary reviewer Signature and Date	

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/s/

Sayed Al-Habet
8/28/2006 03:58:41 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
8/28/2006 04:13:39 PM
BIOPHARMACEUTICS
I concur.

Date: August 17, 2006

From: Jeanne M. Delasko, RN, MS
Label Initiatives Specialist
Study Endpoint and Label Development (SEALD)
Office of New Drugs, CDER

Lilliam A. Rosario, Ph.D.
Senior Pharmacologist, SEALD

Through: Laurie B. Burke, RPh, MPH
Director, SEALD

To: Ladan Jafari
Regulatory Health Project Manager, DPAP

Subject: Proposed Labeling Format Review
NDA 22-051 (fluticasone furoate)

This memo provides a list of revisions for the proposed labeling that should be conveyed to the applicant in the 74-day letter. Please contact Jeanne Delasko (796-0146) or Lilliam Rosario (796-1446) with questions or concerns.

Highlights:

- The drug names must be followed by the drug's dosage form and route of administration. Do not include the dose (i.e., 27.5 mcg). [See 21 CFR 201.57(a)(2)]

- When the labeling is in final draft, the Highlights must be limited in length to one-half page, in 8 point type. [See 21 CFR 201.57(d)(8)]

- The Agency recommends the use of a two-column format for the Highlights and Full Prescribing Information: Contents. [Implementation Guidance]

- We note that Structured Product Labeling (SPL) has been submitted; however, it appears technically inadequate for review. Please contact spl@fda.hhs.gov if you require further assistance.

- Please submit the completed Highlights Data Elements Table. To complete the Highlights data elements, please refer to the following two documents at the FDA Data Standards Council website (http://www.fda.gov/oc/datacouncil) under SPL: "Companion Document for SPL Release 2 Implementation Guide for Highlights DRAFT" and "SPL Highlights Data Element Table." This table must be filled out with the terms that have been proposed for the Highlights data elements. The companion document provides information on the terminology to be used. If you

need assistance completing the Highlights data elements portion of your application, please contact spl@fda.hhs.gov.

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/s/

Jeanne Delasko
8/23/2006 10:38:26 AM
CSO

Lilliam Rosario
8/23/2006 12:55:50 PM
PHARMACOLOGIST

Laurie Burke
8/23/2006 06:54:44 PM
INTERDISCIPLINARY

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: ODS

FROM: Ladan Jafari RPM Division of Pulmonary and Allergy Products
301-796-1231

DATE	IND NO.	NDA NO. 22-051	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT: June 28, 2006
August 3, 2006				

NAME OF DRUG: Allermist (fluticasone furoate nasal spray)	PRIORITY CONSIDERATION: S	CLASSIFICATION OF DRUG: respiratory	DESIRED COMPLETION DATE: February 9, 2007

NAME OF FIRM: GlaxoSmithKline

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☒ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☒ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☒ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☒ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☒ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review the labeling for this new NDA. This is an all electronic submission.

SIGNATURE OF REQUESTER: Ladan Jafari	METHOD OF DELIVERY (Check one) X MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Ladan Jafari
8/3/2006 03:10:05 PM

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*: DDMAC, Michelle Safarik

FROM *(Name, Office/Division, and Phone Number of Requestor)*: Ladan Jafari, RPM Division of Pulmonary and Allergy Products 301-796-1231

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
August 3, 2006		22-051	New NDA	June 28, 2006

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
_____ (fluticasone furoate) Nasal Spray	S	respiratory	February 9, 2007

NAME OF FIRM: GlaxoSmithKline

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Please review the labeling of this new NDA submitted on June 28, 2006. This is an all electronic submission.

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Ladan Jafari	☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Ladan Jafari
8/3/2006 02:55:08 PM

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	PRESCRIPTION DRUG USER FEE COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

GLAXO GROUP LIMITED
Jim McCarthy
One Franklin Plaza 200 N. 16th Street
Philadelphia PA 19101
US

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

22-051

2. TELEPHONE NUMBER
215-751-5923

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

[X] YES [ ] NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

[X] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

[ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

3. PRODUCT NAME
fluticasone furoate

6. USER FEE I.D. NUMBER
PD3006524

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

[ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

[ ] A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE

[ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food,Drug, and Cosmetic Act

[ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] NO

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewinginstructions, 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:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
David M. Cocchetto	US Regulatory Affairs	June 8, 2006

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
$767,400.00

Form FDA 3397 (12/03)

IBE_PRMT_CLOSE_G) (Print Cover sheet)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-051

NDA ACKNOWLEDGMENT

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

Attention: Munir Abdullah, Ph.D.
Director, Regulatory Affairs

Dear Dr. Abdullah:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: fluticasone furoate nasal spray

Review Priority Classification: Standard (S)

Date of Application: June 28, 2006

Date of Receipt: June 29, 2006

Our Reference Number: NDA 22-051

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 28, 2006, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be April 29, 2007.

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 for patients less than 2 years of age. We are waiving the requirement for pediatric studies for this application.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Badrul Chowdhury
7/12/2006 03:34:37 PM

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

FACSIMILE TRANSMITTAL SHEET

DATE: March 6, 2006

To: Munir Abdullah	**From:** Ladan Jafari
Company: GSK	Division of Pulmonary and Allergy Products
Fax number: FAX: 919-315-0033	**Fax number:** 301-796-9728
Phone number: 919-483-9318	**Phone number:** 301-796-1231

Subject: IND 48,647

Total Number of Pages Including Cover: 16

Comments: February 13, meeting minutes

Document to be mailed: ☐ YES ☑ NO

GSK Representatives:

Ed Philpot, Clinical
Kathy Rickard, Clinical
Melissa Faris, Clinical
Jan Osborne, Pre-Clinical Safety
Wei Wu, Statistics
Shu-Yen Ho, Statistics
Geoff Down, Clinical Pharmacology
Barbara McQuade, Project Leader
Paula Rogenes, US Labeling
Rick Rogers, US Regulatory Operations
Elaine Jones, US Regulatory Affairs
Munir Abdullah, US Regulatory Affairs

Division of Pulmonary & Allergy Products (DPAP):

Huiqing Hao, Ph.D., Preclinical Reviewer
Timothy McGovern, Ph.D., Preclinical Supervisor
James Gebert, Ph.D., Biometrics Reviewer
Ruthanna Davi, M.S., Biometrics Team Leader
Shinja Kim, Ph.D., Clinical Pharmacology & Biopharmaceutics Reviewer (by Phone)
Emmanuel Fadiran, Ph.D., Clinical Pharmacology & Biopharmaceutics Team Leader
Amjad Iqbal, Pharm. D., Clinical Pharmacology Fellow
Eugene Sullivan, M.D., Deputy Director
Ladan Jafari, Regulatory Health Project Manager

Office of Drug Evaluation II:

Robert Meyer, M.D., Director

GSK submitted a Pre-NDA meeting request dated November 10, 2005, to discuss the submission of an NDA for fluticasone furoate nasal spray. GSK also submitted a briefing package dated December 19, 2005, which contained a list of questions to be discussed at this meeting. Upon review of the briefing package, the Division responded to GSK's questions via FAX on February 10, 2006. The content of that FAX is printed below. Any discussion that took place at the meeting is captured directly under the relevant original response including any changes in our original position. GSK's questions are in ***bold italics;*** FDA's response is in *Italics;* discussion is in normal font.

Pre-Clinical:

1. ***On the basis of the draft summary data provided in Section 4.8 of the Briefing Document, does the Agency agree that the dose levels selected in the 2-year rat and mouse studies constitute a valid assessment of the carcinogenic potential of fluticasone furoate?***

Response:

We can not agree at this time. No concurrence from the Executive Carcinogenicity Assessment Committee (Exec CAC) was obtained for the dose selection prior to study initiation and the summary data contained in the package provided insufficient information. The reduced survival in female rats and reduced body weight gain indicate an MTD may have been achieved. Of note, changes in absolute body weight should be evaluated rather than changes in body weight gain. The acceptability of the carcinogenicity studies will be determined upon review and evaluation by the Exec CAC.

2. ***The Agency has requested clarification of the significance of a number of findings reported in the fluticasone furoate toxicology studies (FDA fax dated July 26, 2005 and September 1, 2005), and justification of the high dose administered in the second rat micronucleus study. GSK has provided responses to the points raised by the Division and these were submitted to the IND dated November 2, 2005 (Serial No. 0087). Can the Agency confirm that GSK responses to the non-clinical questions have been reviewed and the issues have been adequately addressed and that there are no outstanding non-clinical safety issues for the submission and filing of the planned intranasal fluticasone furoate NDA?***

Response:

We are currently reviewing your submission dated November 2, 2005, and will respond once the review is completed. Based on our preliminary review, the following issues will need to be addressed further: bile tract epithelial vacuolation and nephropathy/kidney tubular basophilia in dogs, eosinophilic inclusions in bronchiolar epithelium in the 6-month rat inhalation study, and adequacy of dosing in the in vivo rat micronucleus assay. We anticipate that final comments will be forwarded by the end of February 2006.

Discussion:

- GSK asked if the Division could elaborate on the concerns regarding the issues identified during the preliminary review. GSK indicated that they plan on submitting the NDA in June, 2006, and asked if they could submit any additional data the Division may require as a minor amendment after the submission of the NDA.

  - The Division indicated that we are still reviewing the data and plan on responding to the November 2, 2005, submission by the end of February or the beginning of March. Once GSK receives our comments, we can discuss any future submissions and how to best address the Division's concerns. The Division stated that we are concerned about the findings that have no NOAEL defined and that are not clinically monitorable. The primary issues of concern for the intranasal program are bile tract epithelial vacuolation and nephropathy/kidney tubular basophilia in dogs, and the adequacy of dosing in the in vivo rat micronucleus assay.

- GSK stated that the finding of bile tract epithelial vacuolation showed a NOAEL in the 9-month dog inhalation study and asked if the intranasal use of this drug is supported.

  - The Division stated that the NOAEL for bile tract epithelial vacuolation in the 9-month dog study needs more deliberation because this finding was also reported in the 3-month inhalation and 6-month intranasal studies in dogs and no NOAEL was defined in these two shorter term studies. The systemic exposures to the test drug in those shorter term studies were similar or lower than that in the 9-month inhalation study. Also, the Division indicated that the data from a single animal that GSK provided as historical control information can not be used to support the assertion that the finding is within background incidence.

- GSK asked if more historical control data can help to alleviate Division's concern.

  - The Division agreed to review additional background data. It was agreed that a database of similar size to that submitted previously to address the kidney findings would be reasonable.

- Regarding the kidney findings, GSK indicated that the effect they see is very mild and there is no clinical significance. GSK also indicated that they believe they can monitor for the clinical sequelae of kidney toxicities by performing routine laboratory tests such as urinalysis in humans.

  ➢ The Division did not agree that clinical monitoring would be sufficient to detect the observed toxicities such as kidney tubular basophilia.

- GSK discussed the micronucleous test in rats, and indicated that they have repeated the test and believe that the highest dose of 4 mg/kg achieved a sufficient dose for the test. Additionally, GSK indicated that they have completed carcinogenicity studies and the results of these studies override the micronucleus test result.

  ➢ The Division referred GSK to the standard protocols for this assay; dosing should achieve the MTD, the maximum feasible dose or a limit dose of 2000 mg/kg. The MTD is defined as the dose producing signs of toxicity such that higher dose levels, based on the same dosing regimen, would be expected to produce lethality. The Division indicated that the highest intravenous dose of 4 mg/kg did not appear to achieve any one of the acceptable criteria stated above.

  ➢ GSK stated that lethality was seen in rats at intravenous doses of 12-18 mg/kg in an acute toxicity study and the dose of 4 mg/kg in the micronucleus test probably reached the maximum tolerated dose.

  ➢ The Division indicated the vehicle used in the acute intravenous study was different from that used in the rat micronucleus test and questioned if the lethality in acute study is related to the vehicle rather than the active drug. The Division stated that we will review the acute dose study to determine if it can be used in the justification for the dose selection in the micronucleus test.

Post meeting note: Review of the rat acute intravenous toxicity study indicates that similar mortality occurred in both vehicle control (10% ethanol + 90% PEG400) and drug treated groups. The lethality observed in this study does not appear to be related to the active drug. Therefore, the lethality in the rat acute intravenous study does not justify the dose selection in the rat micronucleus test.

3. ***In view of the information provided in section 4.12 and 4.13 of the Briefing Document, does the Agency agree that the levels of potential impurities and leachables currently identified in fluticasone furoate nasal spray do not represent a safety concern of patients?***

Response:

Based on the information provided in the table on page 46 of the Pre-NDA CMC package dated December 16, 2005, it is not clear if all identified impurities have been adequately evaluated. As long as the proposed specifications for impurities without structural alerts meet the ICH guidelines regarding qualification thresholds, no further studies will be required. Any impurities exceeding the qualification thresholds should be tested in a 3-month toxicology study and in vitro genotoxicity studies. CDER guidance for genotoxic impurities is under development. However, specifications associated with a limit of — mcg/day for potential genotoxic/carcinogen impurities will likely be acceptable.

Regarding leachables, we acknowledge the PQRI's proposal of qualification thresholds of — mcg/day for leachables with genotoxic/carcinogenic potential and —ncg/day for leachables with general toxicities. The recommendations are not final and have not yet been accepted by the FDA. However, we are considering the proposal in our evaluation of leachable data. Based on the limited information provided, no initial safety concerns have been identified for leachables. A final determination will be made once an NDA is submitted. Any available and relevant safety information should be provided to support proposed acceptance criteria.

4. ***The justification for the use of the inhaled route of administration in the reproductive toxicology studies have been provided in Section 4.6 of the Briefing Document. Does the Agency agree that these studies constitute a valid assessment of the reproductive toxicity potential of fluticasone furoate?***

Response:

We concur. The conducted reproductive toxicity studies are considered valid.

5. ***A list of completed and on-going toxicology studies to be included in the NDA is provided in Attachment 2 in Section 4 of the Briefing Document. At the end of phase 2 (EOP2) meeting (held on July 19, 2004) with the Division of Pulmonary and Allergy Drug Products (DPADP), the Agency reminded GSK***

Response:

With regard to the adequacy of the toxicology package to support the proposed fluticasone furoate nasal spray NDA, assuming that all of the issues identified in response to Question 2 are resolved, we do not anticipate a need for additional preclinical studies for the drug substance.

Clinical Pharmacology & Biopharmaceutics:

6. ***It is usual practice to provide the data relating to pharmacokinetic evaluations as electronic files in the NDA. Since the majority of the data are non-quantifiable (<10 pg/mL), due to the low bioavailability, is there still a requirement to provide electronic data where systemic exposure has been assessed? If so, what is the preferred format? The data is currently available as NONMEM format.***

Response:

Yes, provide all the data that are used for labeling. Submit the data in SAS transport format, and the data related to population PK and PK-PD analyses in NONMEM format.

7. ***It is proposed that the clinical pharmacology safety data are presented and discussed within CTD module 2.7.2. Is this acceptable?***

Response:

The data (files) belong in Module 5, and referenced by Module 2.7.4.

We also have the following additional comment:

We recommend that you add the drug metabolism information you provided on Page 82 of your submission to the 'Metabolism' section under Pharmacokinetics of the package insert.

Clinical/Statistical:

8. ***GSK plans to seek indications for fluticasone furoate nasal spray to treat seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in adult and adolescent subjects age 12 years and older. To support these indications GSK has conducted the clinical development plan outlined in Sections 7 and 8 of this Briefing Document. In this clinical program, at least 1500 adult and adolescent subjects will have been exposed to fluticasone furoate nasal spray at a dose of 100mcg per day or greater. GSK considers this clinical program to be adequate to achieve the indications in SAR and PAR in adult and adolescents. Does the Agency concur?***

Response:

The clinical program described in the briefing document appears adequate to support the submission of an NDA for adults and adolescents. Determination as to whether the program is adequate to support approval and the specific language of the indication will be made during our review of the NDA.

9. ***GSK plans to seek indications for fluticasone furoate nasal spray to treat seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in pediatric subjects age 2 years and older. To support these indications GSK has conducted the clinical development plan outlined in Sections 9 and 10 of this Briefing Document. In this clinical program, at least 864 pediatric subjects will have been exposed to fluticasone furoate nasal spray at a dose of 50mcg or 100mcg per day. GSK considers this clinical program to be adequate to achieve the indications in SAR and PAR in pediatric patients. Does the Agency concur?***

Response:

The clinical program described in the briefing document appears adequate to support the submission of an NDA for children 2-12 years of age. Determinations as to whether the program is adequate to support approval, the appropriateness of the proposed doses, and the specific language of the indication will be made during our review of the NDA.

10. ***In line with our discussions with DPADP, at the EOP2 meeting on 19 July 2004, and pending outcome of our Phase 3 program, we intend to propose the following indication statement:***

    Tradename (fluticasone furoate nasal spray) is indicated for the treatment of the symptoms of seasonal and perennial allergic rhinitis in patients 2 years of age and older.

Does the Agency agree with this indication statement?

Response:

This will be determined during our review of the NDA.

11. ***The efficacy data in the Common Technical Document (CTD) will be summarized in Module 2.7.3, Summary of Clinical Efficacy, as highlighted in Sections 8.4.1 and 11.3.1 of this Briefing Document. A detailed Reporting and Analysis Plan (RAP) for efficacy analysis was submitted to IND 48,647 dated December 2, 2005 (Serial No. 0091) with a request to receive feedback from DPADP by middle of January 2006. In case GSK has not yet received comments and feedback from the Division on our submission of the RAP or if there are any outstanding issues, GSK would like to seek concurrence at the Pre NDA meeting on the efficacy RAP.***

Response:

The RAP is adequate from a statistical perspective with the following suggestion. We prefer that onset in an individual study be defined as the time point from where statistical significance is maintained from that hour onwards rather than allowing one non-significant assessment. Onset of treatment effect for the label will be judged from the collective results of your three SAR studies. The analysis resulting from your proposed definition for onset will be considered; however the final judgment regarding how onset will be described in labeling will be a review issue.

Discussion:

- GSK referred to a response from the Division dated September 13, 2005, which was in response to their submission dated August 29, 2005. GSK indicated that the Division found GSK proposal adequate in September and asked for clarification as to whether or not the thinking has changed.

  - The Division stated that we will take the data from all studies and multiple approaches to the analyses into consideration when looking at labeling onset of action. The Division also indicated that we will consider GSK's suggested definition of onset but we will look at both statistical significance and the level of effect obtained at the assessment times.

12. ***The safety data in the CTD will be summarized in Module 2.7.4, Summary of Clinical Safety, as highlighted in Sections 8.4.2 and 11.3.2 of this Briefing Document. A detailed Reporting and Analysis Plan (RAP) for safety analysis was submitted to IND 48,647 dated December 2, 2005 (Serial No. 0091) with a request to receive feedback from DPADP by middle of January 2006. In case GSK has not yet received comments and feedback from the Division on our submission of the RAP or if there are any outstanding issues, GSK would like to seek concurrence at the Pre-NDA meeting on the efficacy RAP.***

Response:

The RAP is adequate from a statistical perspective.

13. ***In accordance with the ICH and CTD Guidance, GSK is not planning on providing Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS) as separate documents (e.g., in Module 5 of the CTD) but instead will discuss the overall efficacy and safety in Modules 2.7.3 and 2.7.4, respectively, of the CTD as highlighted in Questions #11 and #12 above. Does the Agency agree with this approach?***

Response:

The ISS and ISE are critical components of the submission and are required elements of the NDA submission. They should be included in 5.5.3 (Integrated Analysis of Safety) and ISE (Integrated Analysis of Efficacy), respectively.

Discussion:

- GSK clarified that they will be providing both ISS and ISE, but they were not planning to also include the ISS and ISE in module 5 of the CTD.

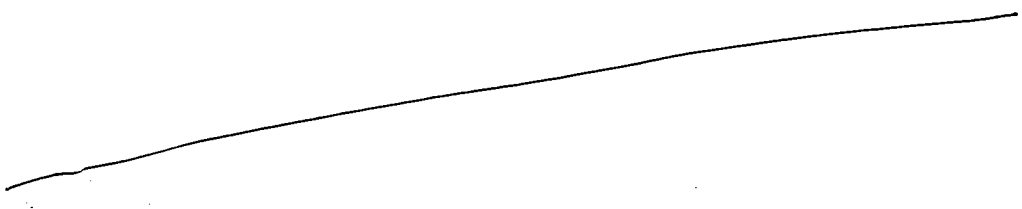
  - The Division indicated that a sufficiently detailed ISS and ISE are integral parts of an application and as long as they are both submitted, there should not be any issues.

14. ***Appendix 7 of the Briefing Document provides summary of studies undertaken to address FDA comments from the EOP2 meeting regarding inclusion of ocular outcomes in the prescribing information. While GSK acknowledges that the final decision on the adequacy of the data to support the ocular efficacy and safety of fluticasone furoate nasal spray will not be made by DPADP until completion of the NDA review, are there any comments the Division would like to share on inclusion of ocular outcomes in the clinical trials section of the prescribing information based on the information provided in this Briefing Document?***

Response:

We have no comments at this time. Labeling language will be determined during our review of the NDA.

15. ***Pending outcome of the safety, efficacy and mechanism of action assessments underway in the Phase 3 program (Appendix 7), GSK intend to include the following language in the Clinical Trials section of the prescribing information (lines 129-133 in the draft prescribing information):***

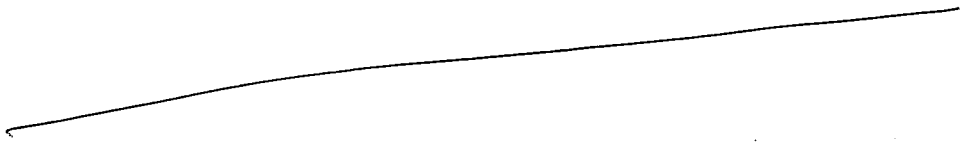


Does the Agency agree that this description of treatment effects on ocular symptoms is appropriate in the Clinical Trials section of the prescribing information?

Response:

Labeling language will be determined during our review of the NDA.

16. ***GSK plans to include the following wording regarding titration of dose in the Dosage and Administration section of the fluticasone furoate prescribing information (lines 354-358 in the draft prescribing information) based on our review and in line with the labeling for currently available intranasal corticosteroids:***



Given fluticasone furoate nasal spray 50mcg once daily was statistically superior to placebo in the dose ranging study FFR20001, does the Agency agree with the inclusion of Individualization of Dosage wording in the prescribing information without the need of any additional clinical data?

Response:

Labeling language will be determined during our review of the NDA.

Discussion:

- GSK clarified that they did not intend this to be a labeling question and rather they want to consider a flexible dose program.

  - The Division stated that the data we have reviewed so far, suggest that 100 mcg was superior to 50 mcg and was considered to be the optimum dose. There do not appear to be any data to establish that patients who achieve control with a dose of 100 mcg will maintain control if the dose is reduced. The Division suggested that GSK put their argument for dose flexibility in the NDA. The Division reminded GSK that dose flexibility is not normally established by dose ranging studies.

17. ***GSK plans to provide patient profiles and the case report forms (CRFs) for subjects who experience death and withdrawals due to adverse events for the adult, adolescent and pediatric phase 2/3 studies listed in Tables 7.1 and 10.1 in the Briefing Document. For all other subjects, CRFs will be available upon request from the Division. In addition, all analysis datasets for studies listed in Section 5.7 (ClinPharm studies) and Tables 7.1 (adult clinical studies) and 10.1 (pediatric clinical studies) will be provided electronically as SAS system transport files (.xpt). Is this acceptable?***

Response:

This is acceptable.

18. ***Based on the last subject last visit date for the long term safety study (FFR102123), the cut-off date for safety information included in the original NDA submission will be 09 December 2005 and 09 April 2006 for the 120 day safety update. In addition to the required safety update from the ongoing studies referenced in the original NDA, the 120 day safety update will include the clinical study report for FFR101888 (thorough QTc study.) Would the Agency expect to see a final safety update prior to the NDA approval?***

Response:

The original NDA submission should contain all of the data deemed necessary to establish the safety and efficacy of the product in support of approval. Safety updates are intended to capture safety information from any use of the product subsequent to the cut-off date for the information included in the original NDA. In addition to the 120-day safety update, we would expect a final safety update.

Discussion:

- GSK indicated that although the systemic exposure is very limited via the intranasal route, they are still planning on including the results of a thorough QTc study in the 120 day safety update. GSK asked if that report is required to be submitted at the time of NDA submission.

  - The Division stated that a thorough QTc study would not be required at the time of NDA submission unless GSK has information to suggest that such a study is a necessary component of the safety database.

General/Other

19. ***Given that the Agency has noted, in its draft Guidance for Industry (September 2005) How to Comply with the Pediatric Research Equity Act (PREA), that "it is the Agency's policy to offer applicants the opportunity to qualify for pediatric exclusivity under section 505 A of the Act for studies required and conducted under PREA," does the Agency agree that the pediatric plan described in Sections 9 and 10 of the Briefing Package is adequate not only to meet the requirement of a "pediatric assessment" under the Pediatric Research Equity Act for SAR and PAR indications for which approval is being sought in adult patients, but also to support issuance of a Section 505A "Written Request" for the new drug fluticasone furoate nasal spray? Recognizing that GSK has, in the described pediatric plan in Sections 9 and 10 of the Briefing Document, outlined the studies it has conducted to demonstrate the safety and efficacy, and dosage and administration of TRADENAME (fluticasone furoate) nasal spray in pediatric patients aged 2 years and older, for the indications of SAR and PAR, will the Agency send GSK a Written Request outlining those same studies, with a submission deadline in 2006 (NDA submission currently planned for June 2006), as the basis for earning pediatric exclusivity for the new drug fluticasone furoate, under*** **Section 505 A of the Act?**

Response:

The Division is discussing this issue with the Division of Pediatric Drug Development. We will respond to this question as soon as possible.

POST-MEETING ADDENDUM:

After consultation with the Division of Pediatric Drug Development, DPAP has determined that it will not issue a Written Request outlining the pediatric studies that have already been performed. DPAP has not yet determined the safety and efficacy of the drug in adults and adolescents, and has not concluded that the pediatric studies utilized the most appropriate doses. Therefore, at the present time there is insufficient evidence that pediatric studies would provide public health benefit.

20. ***The planned dossier for fluticasone furoate nasal spray will be provided in electronic form and will be organized in accordance with ICH guidance to industry. The proposed comprehensive Table of Contents is provided in Appendix 8 of the Briefing Package for the indication of SAR and PAR in adult/ adolescent and pediatrics. Is the proposed format and organization of the dossier acceptable? Given the similarities of SAR and PAR indications, the CTD Sections 2.7.3 (Summary of Clinical Efficacy) and Module 5 (Clinical Study reports) will include information on both SAR and PAR in adult/ adolescent and pediatrics. Does the Agency have any comments on the proposed structuring of Section 2.7.3 and Module 5 of the CTD?***

Response:

We have no comments on this issue.

21. ***An overview of the proposed Risk Management Plan for TRADENMAE (fluticasone furoate nasal spray) is provided in Appendix 9. Information provided includes the pre-marketing risk assessment associated with fluticasone furoate nasal spray and an outline proposal for risk minimization measures for patients using fluticasone furoate nasal spray. Is the proposed Risk Management Plan adequate and acceptable to the Agency?***

Response:

Your proposed plans for pharmacovigilance are acceptable.

Other Issues for Discussion:

- GSK indicated that they plan to submit their NDA for fluticasone furoate nasal spray on June 23, 2006. GSK asked if the Division has any comments regarding their proposal for the trade name ( ) they submitted on December 5, 2005.

  - The Division responded that we have sent a consult to ODS for a tradename review. The Division inquired if GSK has considered the implications of this tradename if they choose to seek an indication for the non-allergic condition, VMR.

-

- GSK indicated that they plan on submitting the labeling for the NDA according to the new Physician Labeling Rule.

    - The Division stated that the Physician Labeling Rule will be in effect on June 30, 2006, so we are not encouraging such submission until the rule is in effect.

Drafted by: LJ/2-16-06

Initialed by: Hao/2-24-06
McGovern/2-24-06
KimSh/2-17-06
Fadiran/2-17-06
Sullivan/2-23-06
Gebert/2-17-06
Davi/2-17-06
Meyer/3-2-06

Filename: I48647Feb13mtgmin.doc

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/s/

Ladan Jafari
3/6/2006 09:06:48 AM

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

FACSIMILE TRANSMITTAL SHEET

DATE: February 6/ 2006

To: Michael Golden	**From:** Ladan Jafari
Company: GSK	Division of Pulmonary and Allergy Drug Products
Fax number: 919-483-5381	**Fax number:** 301-796-9728
Phone number: 919-483-3692	**Phone number:** 301-796-1231
Subject: IND 48,647	
Total no. of pages including cover: 10	

Comments: Pre-NDA CMC meeting minutes

Document to be mailed: ☐ YES ☑ NO

GSK Representatives:

Michael Golden, Director, CMC Regulatory Affairs
Chris Wallis, Ph.D., Director, Synthetic Chemistry Development
Mike Webb, Ph.D., Director, Analytical Sciences
Anna Slater, Manager, Pharmaceutical Development
Gary Cannon, Manager, Pharmaceutical Development
Gregory Webber, Ph.D., Director, Physical Properties & Development

Division of Pulmonary & Allergy Products Representatives:

Arthur Shaw, Ph.D., CMC Reviewer
Prasad Peri, Ph.D., Office of New Drug Quality Assessment (ONDQA) Lead
Richard Lostritto, Ph.D., ONDQA,
Peter Starke, M.D., Medical Team Leader
Miranda Raggio, RN, BSN, MA, Regulatory Health Project Manager
Ladan Jafari, Regulatory Health Project Manager

Background: GSK submitted a Pre-NDA meeting request dated November 7, 2005, to discuss submission of an NDA application for fluticasone furoate nasal spray as it pertains to the CMC section of the application. GSK also submitted a briefing package dated December 16, 2005, which contained a list of questions to be discussed at this meeting. Upon review of the briefing package, the Division responded to GSK's questions via FAX on January 19, 2006. The content of that FAX is printed below. Any discussion that took place at the meeting is captured directly under the relevant original response including any changes in our original position. GSK's questions are in ***bold italics;*** FDA's response is in *Italics;* discussion is in normal font.

1. ***Is the format proposed for the NDA acceptable to the Agency?***

Response:

The proposed eCTD format is appropriate.

2. ***GSK seeks concurrence from the Agency that all the points raised during meetings have been addressed with the exception of the issues listed in Table 1 of the General Topics Section 1.8, which will be addressed in the NDA.***

Response:

At this time we cannot assure you if all past discussion points have been adequately addressed. It is your responsibility to assure that all issues have been addressed in the NDA submission.

7 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Drafted by: LJ/2/2/06

Initialed by: Shaw/2-3-06
Lostritto/2-3-06

Filename: I48647CMCmtgmin.doc

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/s/

Ladan Jafari
2/6/2006 12:22:23 PM

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

FACSIMILE TRANSMITTAL SHEET

DATE: July 30, 2004

To: Munir Abdullah	**From:** Ladan Jafari
Company: GSK	Division of Pulmonary and Allergy Drug Products
Fax number: 919-315-0033	**Fax number:** 301-827-1271
Phone number: 919-483-9318	**Phone number:** 301-827-1084
Subject: IND 48,647	
Total no. of pages including cover: 58	

Comments: End of Phase 2 mtg min.

Document to be mailed: ☐ YES ☑ NO

IND 48,647
Drug: fluticasone furoate nasal spray
Sponsor: GSK
Meeting Date: July 19, 2004
IMTS: 13254, 13255

GSK Representatives:

Susan Spooner, Ph.D., CMC Regulatory Affairs
Chris Beels, Ph.D., Chemical Development
Anna Slater, Pharmaceutical Development
Garry Cannon, New Chemical Entities
Edward Philpot, M.D., Clinical Development
Melissa Faris, Pharm.D., Clinical Development
Richard Stanford, Health Outcomes
Michael Derks, M.D., Ph.D., Clinical Pharmacology
Wei Wu, Ph.D., Clinical Statistics
Paula Rogenes, Ph.D., Product Labeling
Elaine Jones, Ph.D., US Regulatory Affairs
Munir Abdullah, Ph.D., US Regulatory Affairs

Division of Pulmonary & Allergy Drug Products Representatvies:

Katherine Szema, M.D., Medical Reviewer
Peter Starke, M.D., Medical Team Leader
Eugene Sullivan, M.D., Deputy Director
Badrul Chowdhury, M.D., Ph.D., Division Director
Brian Rogers, Ph.D., CMC Reviewer
Richard Lostritto, Ph.D., CMC Team Leader
Huiqing Hao, Ph.D., Preclinical Reviewer
Joe Sun, Ph.D., Preclinical Supervisor
Ruthanna Davi, Ph.D., Biometrics Acting Team Leader
Shinja Kim, Ph.D., Clinical Pharmacology & Biopharmaceutics Reviewer
Sayed Al-Habet, Ph.D., Clinical Pharmacology & Biopharmaceutics Acting Team Leader
Ladan Jafari, Regulatory Project Manager

Background: GSK submitted an End of Phase 2meeting request dated May 13, 2004, to discuss the development plans for GW685698X. GSK requested to have two different meetings to discuss CMC issues separately from the clinical development. Upon review of the request, the Division determined that both meetings could be conducted in one. GSK also submitted a briefing package dated June 18, 2004, which contained a list of questions to be discussed at this meeting. The Division provided the following slides to respond to those questions. Any discussions that followed are printed directly after each relevant slide.

57 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Ladan Jafari
7/30/04 10:07:27 AM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information

NDA 22-051	Efficacy Supplement Type SE-	Supplement Number	
Drug: fluticasone furoate nasal spray		Applicant: GlaxoSmithKline (GSK)	
RPM: Ladan Jafari		HFD-570	Phone # 796-1231

Application Type: **(X)** 505(b)(1) ( ) 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.) **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.** ( ) Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

❖ Application Classifications:	
• Review priority	**(X)** Standard ( ) Priority
• Chem class (NDAs only)	2S
• Other (e.g., orphan, OTC)	
User Fee Goal Dates	April 29, 2007
❖ Special programs (indicate all that apply)	**(X)** None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	**(X)** Paid UF ID number: 3006524
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)
Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes **(X)** No

• This application is on the AIP	( ) Yes (X No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
✓ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	( ) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*	( ) Yes ( ) No
(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *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 (3).*	( ) Yes ( ) No
(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	( ) 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**," 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)? *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).*	( ) Yes ( ) No
(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? (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.*	( ) Yes ( ) No
❖ Exclusivity (approvals only)	
• 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.)	
• 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)*	9/8/2006

General Information	
Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	None
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• 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))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	April 23, 2007
• Most recent applicant-proposed labeling	April 26, 2007
• Original applicant-proposed labeling	June 28, 2006
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DDMAC: January 22, 2007, DSRCS: February 8, 2007 DMETS: March 7, 2007 SEALD: April 24, 2007
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	April 23, 2007
• Applicant proposed	April 26, 2007
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	March 27, 2007
• Documentation of discussions and/or agreements relating to post-marketing commitments	April 11, 2007
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	See attached
❖ Memoranda and Telecons	See attached
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	July 19, 2004
• Pre-NDA meeting (indicate date)	CMC:January 20, 2006 and for all other disciplines: February 13, 2006
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	
• 48-hour alert	
Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	

Summary Application Review	
Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	Medical: March 24, 2007 CMC: April 5, 2007 Preclinical: March 15, 2007
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	August 24, 2006, March 28, 2007
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	October 25, 2006
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	~~N/A~~ February 28, 2007
❖ 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)	July 31, 2006
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	August 23, 2006, February 23, 2007
❖ Biopharmaceutical review(s) *(indicate date for each review)*	August 28, 2006, February 27, 2007
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	August 15, 2006, December 20, 2006, March 28, 2007
Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	December 20, 2006
• 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)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: April 9, 2007 **(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)*	August 28, 2006, March 5, 2007
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	November 15, 2006
❖ CAC/ECAC report	N/A