CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22518Orig1s000

OTHER REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA LABELING REVIEW ADDENDUM

Application number:	22-518
Applicant's letter date:	Email communications dated June 7, 2010 and June 9, 2010
Product:	DULERA (Mometasone Furoate/Formoterol Fumarate)
Indication:	Asthma
Applicant:	Shering Corporation 2000 Galloping Hill Road Kenilworth, NJ 07033
Review Division:	Pulmonary, Allergy, and Rheumatology Products
Reviewer:	Timothy W. Robison, Ph.D., D.A.B.T.
Supervisor/Team Leader:	Molly Topper, Ph.D.
Division Director:	Badrul Chowdhury, M.D., Ph.D.
Project Manager:	Eunice Chung,

Template Version: December 7, 2009

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 22-518 are owned by Schering Corporation or are data for which Schering Corporation has obtained a written right of reference. Any information or data necessary for approval of NDA 22-518 that Schering Corporation does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Schering Corporation does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22-518.

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY

1.1 Recommendations

1.1.1 Approvability
See Review dated January 19, 2010

1.1.2 Additional Non Clinical Recommendations
None

1.1.3 Labeling
The sponsor provided revised labeling in an email dated June 7, 2010. The Division provided the basis of its exposure ratio calculations to the sponsor in a communication dated June 8, 2010. The Sponsor provided clarifications (unit corrections) in an email dated June 9, 2010. With these clarifications, the Division and Sponsor's calculations of exposure ratios (animal dose/exposure to human dose/exposure) are now in agreement. Recommended labeling is provided at the end of this review.

1.2 Brief Discussion of Nonclinical Findings
See Review dated January 19, 2010

2 DRUG INFORMATION

2.1 Drug
DULERA®

2.1.2 Generic Name
Mometasone Furoate + Formoterol Fumarate

2.1.3 Code Name
SCH418131 (Mometasone Furoate + Formoterol Fumarate)

2.1.7 Pharmacologic class
Mometasone furoate: glucocorticoid
Formoterol: β_2-adrenergic agonist

2.2 Relevant IND/s, NDA/s, and DMF/s
Mometasone from Schering: IND 24,088, (b) (4), (b) (4), IND 46,216, IND 52,214, IND 55,108, NDA 19-543, NDA 19-625, NDA 19-796, NDA 20-762, (b) (4) NDA 21-067, (b) (4)

Formoterol from Novartis: NDA 20-831

2.4 Proposed Clinical Population and Dosing Regimen

DULERA is indicated for (b) (4) twice-daily (b) (4) treatment of asthma, (b) (4), in adults and children 12 years of age and older.

2.5 Regulatory Background

The original NDA submission was provided on May 22, 2009. The original PDUFA Goal Date was March 22, 2010. The sponsor submitted a major amendment and the PDUFA Goal Date was extended to June 22, 2010.

3 STUDIES SUBMITTED

3.1 Studies Reviewed

Differences in the results of exposure ratio (animal dose/exposure to human dose/exposure) calculations were noted between the Division and Sponsor, Schering Corporation. For these differences in results, the sponsor provided the basis of their calculations in a submission dated March 5, 2010. A labeling meeting was held with the sponsor on June 4, 2010. Revised labeling was provided by the sponsor in an email dated June 7, 2010. The Division provided the basis of its exposure ratio calculations to the sponsor in a communication dated June 8, 2010 (Date of Labeling Review was June 7, 2010). Additional clarification explaining unit errors was received from the Sponsor in an email dated June 10, 2010. This review examines these clarifications regarding unit errors and is an addendum to the labeling reviews dated May 12, 2010 and June 7, 2010.

11 INTEGRATED SUMMARY AND SAFETY EVALUATION

The Division provided the basis of its exposure ratio calculations to the sponsor in a communication dated June 8, 2010. Additional clarification explaining unit errors was received from the Sponsor in an email dated June 10, 2010. This review examines these clarifications regarding unit errors and is an addendum to the labeling reviews dated May 12, 2010 and June 7, 2010.

(b) (4)

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(b) (4)

[redacted]

Recommended Labeling:

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

DULERA: Teratogenic Effects: Pregnancy Category C
There are no adequate and well-controlled studies of DULERA, mometasone furoate only or formoterol fumarate only in pregnant women. Animal reproduction studies of mometasone furoate and formoterol in mice, rats, and/or rabbits revealed evidence of teratogenicity as well as other developmental toxic effects. Because animal reproduction studies are not always predictive of human response, DULERA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Mometasone Furoate: Teratogenic Effects
When administered to pregnant mice, rats, and rabbits, mometasone furoate increased fetal malformations and decreased fetal growth (measured by lower fetal weights and/or

delayed ossification). Dystocia and related complications were also observed when mometasone furoate was administered to rats late in gestation. However, experience with oral corticosteroids suggests that rodents are more prone to teratogenic effects from corticosteroid exposure than humans.

In a mouse reproduction study, subcutaneous mometasone furoate produced cleft palate at approximately one-third of the maximum recommended daily human dose (MRHD) on a mcg/m^2 basis and decreased fetal survival at approximately 1 time the MRHD. No toxicity was observed at approximately one-tenth of the MRHD on a mcg/m^2 basis.

In a rat reproduction study, mometasone furoate produced umbilical hernia at topical dermal doses approximately 6 times the MRHD on a mcg/m^2 basis and delays in ossification at approximately 3 times the MRHD on a mcg/m^2 basis.

In another study, rats received subcutaneous doses of mometasone furoate throughout pregnancy or late in gestation. Treated animals had prolonged and difficult labor, fewer live births, lower birth weight, and reduced early pup survival at a dose that was approximately 8 times the MRHD on an area under the curve (AUC) basis. Similar effects were not observed at approximately 4 times MRHD on an AUC basis.

In rabbits, mometasone furoate caused multiple malformations (e.g., flexed front paws, gallbladder agenesis, umbilical hernia, hydrocephaly) at topical dermal doses approximately 3 times the MRHD on a mcg/m^2 basis. In an oral study, mometasone furoate increased resorptions and caused cleft palate and/or head malformations (hydrocephaly and domed head) at a dose less than the MRHD based on AUC. At a dose approximately 2 times the MRHD based on AUC, most litters were aborted or resorbed. [*see Nonclinical Toxicology (13.2)*].

Nonteratogenic Effects:
Hypoadrenalism may occur in infants born to women receiving corticosteroids during pregnancy. Infants born to mothers taking substantial corticosteroid doses during pregnancy should be monitored for signs of hypoadrenalism.

Formoterol Fumarate: Teratogenic Effects
Formoterol fumarate administered throughout organogenesis did not cause malformations in rats or rabbits following oral administration. When given to rats throughout organogenesis, oral doses of approximately 80 times the MRHD on a mcg/m^2 basis and above delayed ossification of the fetus, and doses of approximately 2,400 times the MRHD on a mcg/m^2 basis and above decreased fetal weight. Formoterol fumarate has been shown to cause stillbirth and neonatal mortality at oral doses of approximately 2,400 times the MRHD on a mcg/m^2 basis and above in rats receiving the drug during the late stage of pregnancy. These effects, however, were not produced at a dose of approximately 80 times the MRHD on a mcg/m^2 basis.

In another testing laboratory, formoterol was shown to be teratogenic in rats and rabbits. Umbilical hernia, a malformation, was observed in rat fetuses at oral doses approximately 1,200 times and greater than the MRHD on a mcg/m^2 basis. Brachygnathia, a skeletal malformation, was observed in rat fetuses at an oral dose approximately 6,100 times the MRHD on a mcg/m^2 basis. In another study in rats, no teratogenic effects were seen at inhalation doses up to approximately 500 times the MRHD on a mcg/m^2 basis. Subcapsular cysts on the liver were observed in rabbit fetuses at an oral dose approximately 49,000 times the MRHD on a mcg/m^2 basis. No teratogenic effects were observed at oral doses up to approximately 3,000 times the MRHD on a mcg/m^2 basis [*see Nonclinical Toxicology (13.2)*].

10. OVERDOSAGE

10.1 Signs and Symptoms

DULERA: DULERA contains both mometasone furoate and formoterol fumarate; therefore, the risks associated with overdosage for the individual components described below apply to DULERA.

Mometasone Furoate: Chronic overdosage may result in signs/symptoms of hypercorticism *[see Warnings and Precautions (5.7)]*. Single oral doses up to 8000 mcg of mometasone furoate have been studied on human volunteers with no adverse reactions reported.

Formoterol Fumarate: The expected signs and symptoms with overdosage of formoterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the following signs and symptoms: angina, hypertension or hypotension, tachycardia, with rates up to 200 beats/min., arrhythmias, nervousness, headache, tremor, seizures, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, hypokalemia, hyperglycemia, and insomnia. Metabolic acidosis may also occur. As with all inhaled sympathomimetic medications, cardiac arrest and even death may be associated with an overdose of formoterol.

The minimum acute lethal inhalation dose of formoterol fumarate in rats is 156 mg/kg (approximately 63,000 times the MRHD on a mcg/m^2 basis). The median lethal oral doses in Chinese hamsters, rats, and mice provide even higher multiples of the MRHD.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

DULERA: DULERA contains both mometasone furoate and formoterol fumarate; therefore, the mechanisms of actions described below for the individual components apply to DULERA. These drugs represent two different classes of medications (a synthetic corticosteroid and a selective long-acting $beta_2$-adrenergic receptor agonist) that have different effects on clinical, physiological, and inflammatory indices of asthma.

Mometasone furoate: Mometasone furoate is a corticosteroid demonstrating potent anti-inflammatory activity. The precise mechanism of corticosteroid action on asthma is not known. Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to have a wide range of inhibitory effects on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation and in the asthmatic response. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

Mometasone furoate has been shown *in vitro* to exhibit a binding affinity for the human glucocorticoid receptor, which is approximately 12 times that of dexamethasone, 7 times that of triamcinolone acetonide, 5 times that of budesonide, and 1.5 times that of fluticasone. The clinical significance of these findings is unknown.

Formoterol fumarate: Formoterol fumarate is a long-acting selective $beta_2$-adrenergic receptor agonist ($beta_2$-agonist). Inhaled formoterol fumarate acts locally in the lung as a bronchodilator. *In vitro* studies have shown that formoterol has more than 200-fold greater agonist activity at $beta_2$-receptors than at $beta_1$-receptors. Although $beta_2$-receptors are the predominant adrenergic receptors in bronchial smooth muscle and $beta_1$-receptors are the predominant receptors in the heart, there are also $beta_2$-receptors in the human heart comprising 10% to 50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective $beta_2$-agonists may have cardiac effects.

The pharmacologic effects of $beta_2$-adrenoceptor agonist drugs, including formoterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that formoterol is an inhibitor of the release of mast cell mediators, such as histamine and leukotrienes, from the human lung. Formoterol also inhibits histamine-induced plasma albumin extravasation in anesthetized guinea pigs and inhibits allergen-induced eosinophil influx in dogs with airway hyper-responsiveness. The relevance of these *in vitro* and animal findings to humans is unknown.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Mometasone furoate: In a 2-year carcinogenicity study in Sprague Dawley® rats, mometasone furoate demonstrated no statistically significant increase in the incidence of tumors at inhalation doses up to 67 mcg/kg (approximately 14 times the MRHD on an AUC basis). In a 19-month carcinogenicity study in Swiss CD-1 mice, mometasone furoate demonstrated no statistically significant increase in the incidence of tumors at inhalation doses up to 160 mcg/kg (approximately 9 times the MRHD on an AUC basis).

Mometasone furoate increased chromosomal aberrations in an *in vitro* Chinese hamster ovary cell assay, but did not have this effect in an *in vitro* Chinese hamster lung cell assay. Mometasone furoate was not mutagenic in the Ames test or mouse lymphoma assay, and was not clastogenic in an *in vivo* mouse micronucleus assay, a rat bone marrow chromosomal aberration assay, or a mouse male germ-cell chromosomal aberration assay. Mometasone furoate also did not induce unscheduled DNA synthesis *in vivo* in rat hepatocytes.

In reproductive studies in rats, impairment of fertility was not produced by subcutaneous doses up to 15 mcg/kg (approximately 8 times the MRHD on an AUC basis).

Formoterol fumarate: The carcinogenic potential of formoterol fumarate has been evaluated in 2-year drinking water and dietary studies in both rats and mice. In rats, the incidence of ovarian leiomyomas was increased at doses of 15 mg/kg and above in the drinking water study and at 20 mg/kg in the dietary study, but not at dietary doses up to 5 mg/kg (AUC exposure approximately 265 times human exposure at the MRHD). In the dietary study, the incidence of benign ovarian theca-cell tumors was increased at doses of 0.5 mg/kg and above (AUC exposure at the low dose of 0.5 mg/kg was approximately 27 times human exposure at the MRHD). This finding was not observed in the drinking water study, nor was it seen in mice (see below).

In mice, the incidence of adrenal subcapsular adenomas and carcinomas was increased in males at doses of 69 mg/kg and above in the drinking water study, but not at doses up to 50 mg/kg (AUC exposure approximately 350 times human exposure at the MRHD) in the dietary study. The incidence of hepatocarcinomas was increased in the dietary study at doses of 20 and 50 mg/kg in females and 50 mg/kg in males, but not at doses up to 5 mg/kg in either males or females (AUC exposure approximately 35 times human exposure at the MRHD). Also in the dietary study, the incidence of uterine leiomyomas and leiomyosarcomas was increased at doses of 2 mg/kg and above (AUC exposure at the low dose of 2 mg/kg was approximately (b) (4) 14 times human exposure at the MRHD). Increases in leiomyomas of the rodent female genital tract have been similarly demonstrated with other beta-agonist drugs.

Formoterol fumarate was not mutagenic or clastogenic in the following tests: mutagenicity tests in bacterial and mammalian cells, chromosomal analyses in mammalian cells, unscheduled DNA synthesis repair tests in rat hepatocytes and human fibroblasts, transformation assay in mammalian fibroblasts and micronucleus tests in mice and rats.

Reproduction studies in rats revealed no impairment of fertility at oral doses up to 3 mg/kg (approximately 1200 times the MRHD on a mcg/m2 basis).

13.2 Animal Toxicology and/or Pharmacology

Animal Pharmacology
Formoterol fumarate: Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

Reproductive Toxicology Studies
Mometasone furoate: In mice, mometasone furoate caused cleft palate at subcutaneous doses of 60 mcg/kg and above (approximately 1/3 of the maximum recommended human dose MRHD on a mcg/m^2 basis). Fetal survival was reduced at 180 mcg/kg (approximately equal to the MRHD on a mcg/m^2 basis). No toxicity was observed at 20 mcg/kg (approximately one-tenth of the MRHD on a mcg/m^2 basis).

In rats, mometasone furoate produced umbilical hernia at topical dermal doses of 600 mcg/kg and above (approximately 6 times the MRHD on a mcg/m^2 basis). A dose of 300 mcg/kg (approximately 3 times the MRHD on a mcg/m^2 basis) produced delays in ossification, but no malformations.

When rats received subcutaneous doses of mometasone furoate throughout pregnancy or during the later stages of pregnancy, 15 mcg/kg (approximately 8 times the MRHD on an AUC basis) caused prolonged and difficult labor and reduced the number of live births, birth weight, and early pup survival. Similar effects were not observed at 7.5 mcg/kg (approximately 4 times the MRHD on an AUC basis).

In rabbits, mometasone furoate caused multiple malformations (e.g., flexed front paws, gallbladder agenesis, umbilical hernia, hydrocephaly) at topical dermal doses of 150 mcg/kg and above (approximately 3 times the MRHD on a mcg/m^2 basis). In an oral study, mometasone furoate increased resorptions and caused cleft palate and/or head malformations (hydrocephaly and domed head) at 700 mcg/kg (less than the MRHD on an area under the curve [AUC] basis). At 2800 mcg/kg (approximately 2 times the MRHD on an AUC basis) most litters were aborted or resorbed. No toxicity was observed at 140 mcg/kg (less than the MRHD on an AUC basis).

Formoterol fumarate: Formoterol fumarate administered throughout organogenesis did not cause malformations in rats or rabbits following oral administration. When given to rats throughout organogenesis, oral doses of 0.2 mg/kg (approximately 80 times the

MRHD on a mcg/m^2 basis) and above delayed ossification of the fetus, and doses of 6 mg/kg (approximately 2400 times the MRHD on a mcg/m^2 basis) and above decreased fetal weight. Formoterol fumarate has been shown to cause stillbirth and neonatal mortality at oral doses of 6 mg/kg (approximately 2400 times the MRHD on a mcg/m^2 basis) and above in rats receiving the drug during the late stage of pregnancy. These effects, however, were not produced at a dose of 0.2 mg/kg (approximately 80 times the MRHD on a mcg/m^2 basis).

In another testing laboratory, formoterol fumarate was shown to be teratogenic in rats and rabbits. Umbilical hernia, a malformation, was observed in rat fetuses at oral doses of 3 mg/kg/day and above (approximately 1,200 times greater than the MRHD on a mcg/m^2 basis). Brachygnathia, a skeletal malformation, was observed for rat fetuses at an oral dose of 15 mg/kg/day (approximately 6,100 times the MRHD on a mcg/m^2 basis). In another study in rats, no teratogenic effects were seen at inhalation doses up to 1.2 mg/kg/day (approximately 500 times the MRHD on a mcg/m^2 basis). Subcapsular cysts on the liver were observed for rabbit fetuses at an oral dose of 60 mg/kg (approximately 49,000 times the MRHD on a mcg/m^2 basis). No teratogenic effects were observed at oral doses up to 3.5 mg/kg (approximately 3,000 times the MRHD on a mcg/m^2 basis).

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22518	ORIG-1	SCHERING CORP	MOMETASONE FUROATE/FORMOTEROL FUMARATE

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/s/

TIMOTHY W ROBISON
06/10/2010

MOLLY E SHEA
06/10/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	June 08, 2010
To:	Badrul Chowdhury, M.D. Director **Division of Pulmonary, Allergy, and Rheumatology Products**
Through:	Claudia Karwoski, PharmD, Director **Division of Risk Management (DRISK)** LaShawn Griffiths, MSHS-PH, BSN, RN Patient Labeling Reviewer, Acting Team Leader **Division of Risk Management**
From:	Latonia M. Ford, RN, BSN, MBA Patient Labeling Reviewer **Division of Risk Management (DRISK)**
Subject:	DRISK Review of Patient Labeling (Medication Guide)
Drug Name(s):	Dulera (mometasone furoate and formoterol fumarate) inhalation aerosol
Application Type/Number:	NDA 22518
Applicant/sponsor:	Schering Plough Corporation
OSE RCM #:	2009-1099

1 INTRODUCTION

This review is written in response to a request by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) Dulera (mometasone furoate and formoterol fumarate).

2 BACKGROUND

Schering-Plough Corporation submitted an original 505 (b) (1) New Drug Application, NDA 22518, for Dulera (mometasone furoate and formoterol fumarate) inhalation aerosol on May 21, 2009. The proposed indication is for (b) (4) treatment of asthma in adults and children 12 years of age and older. Dulera combines an inhaled corticosteroid medicine, mometasone furoate (the same medicine found in Asmanex Twisthaler), and a long-acting beta2-agonist medicine (LABA), formoterol (the same medicine found in Foradil Aerolizer).

On February 18, 2010, the Agency issued Prior Approval Supplement Request Letters to all of the sponsors of long acting beta agonists (LABAs) notifying them to submit safety labeling changes (SLC) and a proposed Risk Evaluation and Mitigation Strategy (REMS). The letter was issued to address the risk of serious asthma outcomes associated with the use of these products. Schering Plough was notified at the same time to submit a REMS amendment for Dulera.

On March 5, 2010, Schering Plough submitted a proposed REMS amendment for Dulera that includes a Medication Guide, Communication Plan, and a timetable for submission of assessment of the REMS.
The proposed REMS is currently under review by DRISK. Interim comments on the proposed REMS were provided under a separate cover.

Please let us know if DPAP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

3 MATERIAL REVIEWED

- Draft Dulera (mometasone furoate and formoterol fumarate) inhalation aerosol Prescribing Information (PI) submitted May 21, 2009, and revised by the Review Division throughout the review cycle and provided to DRISK on May 25, 2010
- Draft Dulera (mometasone furoate and formoterol fumarate) inhalation aerosol Medication Guide submitted May 21, 2009

4 RESULTS OF REVIEW

In our review of the MG and IFU, we:

- referenced the labeling (PIs and MGs) for ADVAIR HFA, ADVAIR DISKUS, and SYMBICORT in the Supplement Order Letters dated June 2, 2010.

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG meets the regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated MG is appended to this memo. Any additional revisions to the PI should be reflected in the MG and IFU.

Please let us know if you have any questions.

31 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22518	ORIG-1	SCHERING CORP	MOMETASONE FUROATE/FORMOTEROL FUMARATE

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/s/

LATONIA M FORD

06/08/2010

Dulera (mometasone furoate and formoterol fumarate) inhalation aerosol NDA 22518
DRISK Review of Patient Labeling (Medication Guide)

CLAUDIA B KARWOSKI

06/08/2010

concur

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

PHARMACOLOGY/TOXICOLOGY LABELING REVIEW

NDA NUMBER:	**22-518**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**05/22/09**
PRODUCT:	**DULERA (Mometasone Furoate/Formoterol Fumarate)**
INTENDED CLINICAL POPULATION:	**Asthma**
SPONSOR:	**Shering Corporation** **2000 Galloping Hill Road** **Kenilworth, NJ 07033**
DOCUMENTS REVIEWED:	**Electronic Submission**
REVIEW DIVISION:	**Division of Pulmonary and Allergy Products (HFD-570)**
PHARM/TOX REVIEWER:	**Timothy W. Robison, Ph.D., D.A.B.T.**
PHARM/TOX SUPERVISOR:	**Molly Shea, Ph.D.**
DIVISION DIRECTOR:	**Badrul Chowdhury, M.D., Ph.D.**
PROJECT MANAGER:	**Eunice Chung, Pharm.D.**
Date of review submission to DARRTS:	**May 12, 2010**

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability
See Review dated January 19, 2010

B. Recommendation for nonclinical studies
See Review dated January 19, 2010

C. Recommendations on labeling
The sponsor submitted proposed labeling in general conformance with 21 CFR Part 201 (April 1, 2009).

Changes were made to Sections 8.1 to include required information that the sponsor placed in Section 13.2 and to update information to provide patients with accurate information regarding the known teratogenicity of formoterol.

All calculations of animal to human exposure ratios are relative to the highest proposed clinical dose of Dulera® (MF/F) at 400/10 mcg BID.

Labeling for mometasone furoate:
Nonclinical labeling sections from Asmanex® (NDA 21-067) were used for nonclinical labeling section specific to the mometasone component of Dulera®.

(b) (4)

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22518	ORIG-1	SCHERING CORP	MOMETASONE FUROATE/FORMOTEROL FUMARATE

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/s/

TIMOTHY W ROBISON
05/12/2010

MOLLY E SHEA
05/12/2010

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

PHARMACOLOGY/TOXICOLOGY NDA LABELING REVIEW ADDENDUM

Application number:	22-518
Applicant's letter date:	March 5, 2010
CDER stamp date:	March 5, 2010
Product:	DULERA (Mometasone Furoate/Formoterol Fumarate)
Indication:	Asthma
Applicant:	Shering Corporation 2000 Galloping Hill Road Kenilworth, NJ 07033
Review Division:	Pulmonary, Allergy, and Rheumatology Products
Reviewer:	Timothy W. Robison, Ph.D., D.A.B.T.
Supervisor/Team Leader:	Molly Topper, Ph.D.
Division Director:	Badrul Chowdhury, M.D., Ph.D.
Project Manager:	Eunice Chung,

Template Version: December 7, 2009

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 22-518 are owned by Schering Corporation or are data for which Schering Corporation has obtained a written right of reference. Any information or data necessary for approval of NDA 22-518 that Schering Corporation does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Schering Corporation does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22-518.

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY

1.1 Recommendations

1.1.1 Approvability

See Review dated January 19, 2010

1.1.2 Additional Non Clinical Recommendations

None

1.1.3 Labeling

Differences in the results of exposure ratio (animal dose/exposure to human dose/exposure) calculations were noted between the Division and sponsor, Schering Corporation. For these differences in results, the sponsor provided the basis of their calculations in a submission dated March 5, 2010. This review examines these differences in calculations and is an addendum to the labeling review dated May 12, 2010.

Comments to Sponsor: The following comments should be conveyed to the sponsor.

Your submission dated March 5, 2010 is currently under review and we have the following comments.

1. For calculations of exposure ratios for mometasone furoate with respect to reproductive toxicology studies described in Sections 8.1, 13.1, and 13.2, we agree with your calculations and have revised the labeling accordingly.

2. For calculations of exposure ratios for mometasone furoate with respect to the rat and mouse carcinogenicity studies described in Section 13.1, we are not able to agree with your calculations at this time and the labeling has not been changed.

a. Clarify the statement that (b) (4) refer to and how were these numbers obtained.

b. Clarify the statement that (b) (4) refer to and how were these numbers obtained.

3. For calculations of exposure ratios for formoterol fumarate with respect to the rat and mouse carcinogenicity studies described in Section 13.1, we are not able

to agree with your calculations at this time and the labeling has not been changed.

We are providing the basis of our calculations below.

The labeling for Foradil® Aerolizer™ has been essentially retained for the labeling sections specific to the formoterol component of DULERA®; however, adjustments have been inserted to take into account differences in systemic drug exposure.

(b) (4)

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(b) (4)

1.2 Brief Discussion of Nonclinical Findings

See Review dated January 19, 2010

2 DRUG INFORMATION

2.1 Drug

DULERA®

2.1.2 Generic Name

Mometasone Furoate + Formoterol Fumarate

2.1.3 Code Name

SCH418131 (Mometasone Furoate + Formoterol Fumarate)

2.1.7 Pharmacologic class

Mometasone furoate: glucocorticoid
Formoterol: β_2-adrenergic agonist

2.2 Relevant IND/s, NDA/s, and DMF/s

Mometasone from Schering: IND 24,088, (b) (4), (b) (4), IND 46,216, IND 52,214, IND 55,108, NDA 19-543, NDA 19-625, NDA 19-796, NDA 20-762, (b) (4) NDA 21-067, (b) (4)

Formoterol from Novartis: NDA 20-831

2.4 Proposed Clinical Population and Dosing Regimen

DULERA is indicated for (b) (4) twice-daily (b) (4) treatment of asthma, (b) (4), in adults and children 12 years of age and older.

2.5 Regulatory Background

The original NDA submission was provided on May 22, 2009. The original PDUFA Goal Date was March 22, 2010. The sponsor submitted a major amendment and the PDUFA Goal Date was extended to June 22, 2010.

3 STUDIES SUBMITTED

3.1 Studies Reviewed

Differences in the results of exposure ratio (animal dose/exposure to human dose/exposure) calculations were noted between the Division and sponsor, Schering Corporation. For these differences in results, the sponsor provided the basis of their calculations in a submission dated March 5, 2010. This review examines these differences in calculations and is addendum to the labeling review dated May 12, 2010.

11 INTEGRATED SUMMARY AND SAFETY EVALUATION

Differences in the results of exposure ratio (animal dose/exposure to human dose/exposure) calculations were noted between the Division and sponsor, Schering Corporation. For these differences in results, the sponsor provided the basis of their calculations in a submission dated March 5, 2010. This review examines these differences in calculations and is an addendum to the labeling review dated May 12, 2010. Recommended labeling is provided at the end of this review.

(b) (4)

11 pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22518	ORIG-1	SCHERING CORP	MOMETASONE FUROATE/FORMOTEROL FUMARATE

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/s/

TIMOTHY W ROBISON
06/07/2010
Labeling comments to sponsor

MOLLY E SHEA
06/07/2010

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Pulmonary and Allergy Products

Application Number: NDA 22-518

Name of Drug: Dulera (mometasone furoate/formoterol fumarate)

Applicant: Schering Plough

Material Reviewed:

Submission Date(s): March 5, 2010

Receipt Date(s): March 8, 2010

Submission Date of Structure Product Labeling (SPL): N/A

Type of Labeling Reviewed: PLR (PDF)

Background and Summary

This review was for the proposed PLR labeling, received March 8, 2010, from Schering Plough which was a response to the Division's labeling comments, dated February 18, 2010.

Review

The following issues/deficiencies with regard to format have been identified in the Highlights section of your proposed labeling.

Highlights Section:

1. Place the date of the most recent revision of the labeling at the end of the Highlights section. The preferred format is "Revised: Month Year: or "Revised: Month/Year."

2. The Highlights section should be limited to the the one-half page requirement for Highlights (Highlights, excluding any Boxed Warning, are limited in length to one-half page if printed on 8.5" x 11 paper, single spaced, with 8-point type and ½ inch margin.) The sponsor has requested a waiver in their original application. According to the PLR FAQs #10, Requests to waive the one-half page requirement for Highlights should not be forwarded to the waiver's committee. OND's response to this type of waiver request will be determined by the review division during the review process.

If, during the review, the review division determines that HLs should exceed the ½ page limit, the review division may approve the waiver. CSL provides language to include in the approval letter stating whether the waiver was granted or denied.

Table of Contents:

3. Remove periods after numbers for section headings in the Table of Contents Section.

4. The same title for the boxed warning that appears in the Highlights and Full Prescribibg Information must also appear at the beginning of the Table of Contents in upper-case letters and bold type. For example: **WARNING: ASTHMA-RELATED DEATH.**

Full Prescribing Information

5. Add the following statement at the end of the Table of Contents: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

6. Remove periods after numbers for all section headings throughout the Full Prescribing Information.

7. Remove bold type for any non-section or non-subsection headings throughout the Full Prescribing Information.

Recommendations

The format issues indicated in the review will be conveyed at the labeling meeting #2 that will take place on May 28, 2010.

_____
Eunice H. Chung, Pharm.D
Regulatory Project Manager

Supervisory Comment/Concurrence:

Sandy L. Barnes
Chief, Project Management Staff

Drafted: EC/5MAY2010
Revised/Initialed: SB/11MAY2010
Finalized: EC/12MAY2010
Filename: CSO Labeling Review Template (updated 1-16-07).doc

CSO LABELING REVIEW OF PLR FORMAT

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22518	ORIG-1	SCHERING CORP	MOMETASONE FUROATE/FORMOTEROL FUMARATE

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/s/

EUNICE H CHUNG
05/12/2010

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: January 25, 2010

TO: Eunice Chung, PharmD, Regulatory Project Manager
Susan Limb, M.D., Medical Officer
Division of Pulmonary and Allergy Products Products

THROUGH: Tejashri Purohit-Sheth, MD
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

FROM: Anthony Orencia, MD, FACP
Medical Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-518

APPLICANT: Schering-Plough Corporation

DRUG: mometasone furoate/formoterol drug combination

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: (b) (4) twice-daily (b) (4) treatment of asthma, (b) (4) in adults and children 12 years and older.

CONSULTATION REQUEST DATE: July 16, 2009

DIVISION ACTION GOAL DATE: March 22, 2010

PDUFA DATE: March 22, 2010

I. **BACKGROUND**:

Concomitant therapy with inhaled glucocorticosteroids (ICS) plus long-acting beta agonists (LABA) in the management of moderate-to-severe persistent asthma is well established. In patients receiving ICS whose asthma is not fully controlled, increasing the dose of ICS or, alternatively, adding a LABA to the current dose of ICS, are two therapeutic options. Multiple inhalers for concurrent administration of different asthma medications have evolved into the availability of single inhalers with combination treatments. This may reduce the complexity of using multiple inhalers, the risk of treating with LABA without concomitant ICS, and improving compliance with better asthma control.

Two pivotal studies were submitted in support of this application as below.

Protocol P04334:

Protocol P04334 was a randomized, multi-center, double-blind, double-dummy, placebo-controlled, parallel group study. The study was initiated on November 27, 2006 and completed on October 10, 2008. There were 152 study centers worldwide ((North America (270 subjects), Latin America (95 subjects), Asia (111 subjects), Europe (211 subjects), Ukraine (53 subjects), and Russia (41 subjects)), where 781 subjects were randomized and enrolled to double-blinded treatment in this study, and 551 study subjects completed the study. All randomized subjects received at least one dose of double-blind study medication, except for one subject in the placebo group where there was no record of treatment. The co-primary objectives were two-fold: (1) To determine the efficacy of mometasone furoate/formoterol fumarate (MF/F) metered dose inhaler (MDI) 200/10 mcg twice daily (BID) compared with MF MDI 200 mcg BID, in order to assess the added benefit of formoterol (F) MDI 10 mcg BID to the combination, and (2) To determine the efficacy of mometasone furoate (MF)/formoterol (F) MDI 200/10 mcg BID compared with F MDI 10 mcg BID, in order to assess the benefit of the steroid component (MF MDI 200 mcg BID) to the combination.

Protocol P0473:

Protocol P0473 was a randomized, multi-center, double-blind, double-dummy, placebo-controlled, parallel group study. The study was initiated on November 17, 2006 and completed on October 17, 2008. There were 172 study sites worldwide, the majority in the United States (54 subjects) and India (24 subjects)), where 746 subjects were randomized and enrolled to double-blinded treatment in this study, and 536 study subjects completed the study. The co-primary objectives were two-fold: (1) To determine the efficacy of mometasone furoate/formoterol fumarate (MF/F) metered dose inhaler (MDI) 100/10 mcg twice daily (BID) compared with MF MDI 100 mcg BID, in order to assess the added benefit of formoterol (F) MDI 10 mcg BID to the combination, and (2) To determine the efficacy of mometasone furoate (MF)/formoterol (F) MDI 100/10 mcg BID compared with F MDI 10 mcg BID, in order to assess the benefit of the steroid component (MF MDI 100 mcg BID) to the combination.

The co-primary efficacy endpoints for Protocol P0473 are similar to that of Protocol P0443. The co-primary efficacy endpoints were the following: (1) The AUC(0-12 hr) of the change from Baseline to Week 12 in FEV1 for the comparison of mometasone furoate (MF)/formoterol (F) vs mometasone furoate (MF). The average of the two pre-dose FEV1 measurements (30 minutes prior to dosing and 0 hour, immediately prior to dosing) at the Baseline Visit were subtracted from each of the serial measurements over the 12-hour period. The AUC was calculated based on these changes from baseline evaluations, and (2) Time-to-first severe asthma exacerbation over the 26-week Treatment Period for the comparison of mometasone furoate (MF)/formoterol (F) vs formoterol (F).

Two clinical sites (Drs. Nayak and Kerwin, respectively) were inspected for this study, as well as the sponsor, Schering-Plough.

II. RESULTS (by protocol/site):

Name of CI and site #, if known	City, State	Protocol(s)	Inspection Date	EIR Received Date	Final Classification
Anjuli Nayak, MD /Site #16	Normal, IL	P04334 P04073	September 10-21, 2009	November 3, 2009	NAI
Edward Kerwin, MD /Site #12	Medford, OR	P04334 P04073	September 14-18, 2009	October 16, 2009	Pending Preliminary field classification: VAI
Schering-Plough Corporation	Kenilworth, NJ	Sponsor	September 23 to October 23, 2009	November 18, 2009	Pending Preliminary field classification: VAI

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability
OAI = Significant deviations for regulations. Data unreliable.
Pending= The EIR has not been received and findings are based on preliminary communication with the field.

PROTOCOLS P04073 and P04334
Both Protocols P0473 and P04334 were investigated at the clinical sites for Drs. Nayak and Kerwin. A major difference between Protocol P04334 and Protocol P0473 was in the dose that persistent asthma subjects received: higher or lower dose of inhaled glucocorticosteroids. P04334 enrolled subjects taking medium-dose inhaled steroids while P0473 enrolled subjects taking low-dose inhaled steroids.

1. Anjuli Nayak, MD/Site 16

Sneeze, Wheeze & Itch Associates, LLC
2010 Jacobssen Drive
Normal, IL 61761

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from September 9 to 15, 2009. For Protocol #P04073, there were 20 subjects enrolled and

11 subjects randomized. Nine subjects withdrew or were discontinued due to asthma exacerbation (n=4), serious adverse event (n=1), noncompliance (n=1) and withdrawal of consent (n=2). For Protocol # P04334, there were 20 subjects enrolled and 14 randomized. Six subjects withdrew and were discontinued from the study, due to asthma exacerbation (n=1), prednisone use (n=2), and protocol deviation (n=1). There were no deaths reported for both studies. Audits of four subjects' records for Protocol #P04073 and five subjects' records for Protocol # P04334 were conducted, respectively. No issues were noted for the efficacy endpoints in P04334 and P0473, respectively.

The inspection evaluated the following documents: comparison of medical records to electronic case report forms, audit trails for spirometry testing electronic data, study drug accountability logs, informed consent documents, study monitoring visits and correspondence. Source documents were verified for consistency with data listings.

b. Limitations of inspection:
None.

c. General observations/commentary:
Study randomization and blinding procedures were followed. No significant regulatory violations were noted and no Form FDA 483 was issued.

d. Data acceptability/reliability for consideration in the NDA review decision:
The data in support of clinical efficacy and safety at this clinical site appear acceptable.

2. Edward Kerwin, MD/**Site #12**
Clinical Research Institute of Southern Oregon, PC
3860 Crater Lake Ave., Suite B
Medford, OR 97504

a. What was inspected?
The inspection was conducted in accordance with Compliance Program 7348.811, from September 14 to 18, 2009.

For Protocol P04073, a total of 22 subjects were screened; 18 subjects were randomized and 13 subjects completed the study. For Protocol 04334, a total of 13 subjects were screened, 11 subjects were randomized and 7 subjects completed the study.

The inspection evaluated the following: data collection, data reporting, consent forms, electronic data and source document components, and investigational product accountability. Viasys Health Care provided ambulatory monitoring systems for various asthma measures captured electronically.

b. Limitations of inspection:
None.

c. General observations/commentary:
Although the ORA field office classified this clinical site inspection as VAI, no FDA Form 483 was issued. This was referred to DSI for review and final classification.

Inspectional findings for each study are as follows:

For Study P0473, there were no deficiencies in informed consent documentation. For each subject file reviewed, 14 patients were assessed for patient eligibility, electronic diary not below specified limits, spirometry data for the specified visits, completion of investigator and coordinator progress notes, adverse events, concomitant drug logs, presence of chest x-ray within the past year, and asthma patient-reported outcome surveys. A few isolated deficiencies were noted.

- Subject 0212 had accidental peanut ingestion on 11/1/07, with patient-reported wheezing that was relieved by albuterol 3 weeks prior to visit #10. The study sub-investigator noted this incident was not reported as an adverse event by patient to clinical coordinator.

- Subject 0674's electronic diary showed 3 separate morning peak expiratory flow (PEF) below stability limits (2/7-2/9, 2008) and 2 separate afternoon PEF readings below stability limits (2/7-2/8, 2008) but the study coordinator's progress notes did not note this as an asthma exacerbation, which the clinical investigator agreed with the field investigator as the case.

For Study P04334, all informed consent documents were signed and dated prior to performing any procedures in the study. For each subject file reviewed, 13 patients were assessed for patient eligibility, electronic diary not below specified limits, spirometry data for the specified visits, completion of investigator and coordinator progress notes, adverse events, concomitant drug logs, presence of chest x-ray within the past year, and asthma patient-reported outcome surveys. No significant issues were noted for the conduct of this study.

d. Data acceptability/reliability for consideration in the NDA review decision:
While minor deficiencies in adherence to protocol were observed for Study P0473 , these observations do not appear to have a substantive impact on data integrity and patient safety. The data in support of clinical efficacy and safety from this clinical site appear acceptable.

3. Schering-Plough Corporation/Sponsor
2000 Galloping Hill Road
Kenilworth, NJ 07033-0530

a. What was inspected?
The inspection was conducted in accordance with Compliance Program 7348.810 from September 23 to October 23, 2009. The inspection evaluated the following documents: structural organization, clinical study sites, and master services agreements. Clinical trial monitoring included the following: project management, development of country-specific informed consent forms, patient tools and translations, global pharmaco-vigilance and preparation/submission of documents for regulatory approval internationally, except for (b) (4) which was contracted to and conducted by (b) (4). The trial-independent Institutional Review Board was (b) (4).

b. Limitations of inspection:
None.

c. General observations/commentary:
A one-observation Form FDA 483 was issued on 10/23/2009 at the end of the inspection for failure to ensure proper monitoring of the study, with specific deficiencies to both Protocols P04703 and P04334, respectively, albeit no substantive regulatory violations were noted. Schering Plough responded to these specific deficiencies as part of their continuous improvement action plan in a letter received on 11/10/2009.

For Protocol 04073, the following regulatory deficiencies were noted:

- At Site 16, monitoring visit report of 3/14/2007, 8/14/2007, and 8/11- 8/12/2008 documented that the review of Investigational Product (storage, handling and documentation) was not performed. Further, at Site 12, monitoring visit of 8/7/2007, documented that review of Investigational Product (storage, handling and documentation) was not performed.

For Protocol 04334, the following regulatory deficiencies were noted:

- At Sites 12 and 16, the clinical trial CRO did not notify the IRB that the Informed Consent Form of 10/11/2007 had incorrect run-in dosage information (50 mcg versus 100 mcg).
- At Site 16, monitoring visit report of 8/15/2007, 10/10/2007, and 8/11-8/12, 2008 documented that the review of Investigational Product (storage, handling and documentation) was not performed.

d. Data acceptability/reliability for consideration in the NDA review decision:
While minor regulatory observations were noted as above regarding proper informed consenting of study subjects and documentation related at the site monitoring visit reports, these do not appear to have a significant impact on data integrity and patient safety of these clinical trials. The data in support of clinical efficacy and safety at this clinical site appear acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Two domestic clinical investigator sites and the sponsor were inspected in support of this application for study Protocols P04073 and P04334, in support of mometasone and formoterol combination for (b) (4) treatment of asthma.

Inspection findings documented adherence to Good Clinical Practices regulations governing the conduct of clinical investigations. Although minor regulatory violations were noted, these are isolated in nature, and are unlikely to impact data integrity. The data generated by these inspected sites appear reliable in support of the application.

{See appended electronic signature page}

Anthony Orencia, M.D.
Medical Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22518	ORIG-1	SCHERING CORP	MOMETASONE FUROATE/FORMOTEROL FUMARATE

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/s/

ANTHONY J ORENCIA
01/27/2010

TEJASHRI S PUROHIT-SHETH
01/27/2010

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-518 Supplement # 000 Efficacy Supplement Type SE-

Proprietary Name: DULERA®
Established Name: mometasone furoate/formoterol fumarate Inhalation Aerosol
Strengths: (b) (4) 100/5 and 200/5 microgram

Applicant: Schering Plough
Agent for Applicant (if applicable): N/A

Date of Application: May 21, 2009
Date of Receipt: May 22, 2009
Date clock started after UN:
Date of Filing Meeting: July 6, 2009
Filing Date: July 21, 2009 (74 day letter due August 4, 2009)
Action Goal Date (optional): User Fee Goal Date: March 22, 2009

Indication(s) requested: (b) (4) twice-daily (b) (4) treatment of asthma, (b) (4), in adults and children 12 years of age and older.

Type of Original NDA: (b)(1) ☒ (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 ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 4
Other (orphan, OTC, etc.)

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

User Fee Status: Paid ☒ 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 ☐ NO ☒
  If yes, explain:

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 ☒

- 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 ☒
  If yes, explain:

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

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

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

- Submission complete as required under 21 CFR 314.50? YES ☒ 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 ☐
   This application is: All electronic ☒ 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 ☒ 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 ☒ NO ☐

- Exclusivity requested? YES, 3 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 ☒ 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 ☒ 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 ☒

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES ☒ 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 ☒ NO ☐

- PDUFA and Action Goal dates correct in tracking system? YES ☒ 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. *(emailed DRTL)*

- List referenced IND numbers: IND 70, 283

- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☒
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) December 15, 2008 NO ☐
If yes, distribute minutes before filing meeting. PIND Meeting 11/3/04

- Any SPA agreements? Date(s) _____ NO ☒
  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 ☒ 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 ☒ 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 ☒ NO ☐

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

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

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

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

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ 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 ☒ NO ☐

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

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 6, 2009

NDA #: 22-518

DRUG NAMES: Dulera (mometasone furoate/formoterol fumarate)

APPLICANT: Schering Plough

BACKGROUND: Schering Plough has submitted a New Drug Application for DULERA® (mometasone furoate/formoterol fumarate) Inhalation Aerosol (b) (4) 100/5 and 200/5 microgram, with the following indication: The sponsor's proposed indication is for (b) (4) twice-daily (b) (4) treatment of asthma, (b) (4) in adults and children 12 years of age and older. Dulera is a metered dose inhaler combining two drug substances which have been previously approved for administration via oral inhalation for the treatment of asthma: mometasone furoate inhalation powder (Asthmanex Twisthaler110 and 220 mcg) and formoterol fumarate inhalation powder (Foradil Aerolizer 12 mcg).

ATTENDEES:
Badrul Chowdhury, M.D., Ph.D., Director, DPAP
Sally Seymour, M.D., Deputy Director for Safety, DPAP
Susan Limb, M.D., Clinical Reviewer, DPAP
Tim Robison, Ph.D., Nonclinical Reviewer, DPAP
Molly Shea, Ph.D., Nonclinical Reviewer, DPAP
Jean Wu, M.D., Ph.D., Acting Nonclinical Supervisor, DPAP
Ying Fan, Ph.D., Clinical Pharmacology Reviewer, DPAP
Partha Roy, Ph.D., Acting Clinical Pharmacology Team Leader, DPAP
Alan Schroeder, Ph.D., Product Quality Reviewer, ONDQA, Branch II
Prasad Peri, Ph.D., Pharmaceutical Assessment Lead, ONDQA, Branch II
Ali Al Hakim, Ph.D., Chief, ONDQA, Branch II
Robert Abugov, Ph.D., Statistical Reviewer, Division of Biometrics II
Qian Li, Ph.D., Statistical Team Leader, Division of Biometrics II
Ladan Jafari, Safety Project Manager, DPAP
Wayne Amchin, Regulatory Project Manager, DDMAC
LCDR Deveonne Hamilton-Stokes, RN, BSN, Safety Evaluator, OSE, DMEPA

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization	**Reviewer**
Medical:	Susan Limb
Secondary Medical:	Sally Seymour
Statistical:	Robert Abugov
Pharmacology:	Ying Fan
Statistical Pharmacology:	
Chemistry:	Alan Schroeder/Prasad Peri
Environmental Assessment (if needed):	
Biopharmaceutical:	
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	Anthony Orencia

OPS:
Regulatory Project Management: Eunice Chung
Other Consults: Deveonne Hamilton-Stokes/Todd Bridges (OSE)
Jessica Adams/Sangeeta Vaswani (DDMAC)

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

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☒ NO ☐
  If no, explain:
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒

- 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 ☒ YES ☐ NO ☐

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

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

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

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

- GLP audit needed? YES ☐ NO ☐

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

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

ELECTRONIC SUBMISSION: yes
Any comments:

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

☐ The application is unsuitable for filing. Explain why:

☒ 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.

☒ 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.

Eunice H. Chung, Pharm.D.
Regulatory Project Manager

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22518	ORIG-1	SCHERING CORP	MOMETASONE FUROATE/FORMOTEROL FUMARATE

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/s/

EUNICE H CHUNG
01/15/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	December 7, 2009
To:	Badrul Chowdhury, MD, Director Division of Pulmonary and Allergy Products
Through:	Todd Bridges, RPh, Team Leader Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Deveonne Hamilton-Stokes, RN, BSN, Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Label and Labeling Review
Drug Name(s):	Dulera (Mometasone Furoate and Formoterol Fumarate Dihydrate) Inhalation Aerosol (b) (4), 100 mcg/5 mcg and 200 mcg/5 mcg
Application Type/Number:	NDA 22-518 (IND 70,283)
Applicant:	Schering-Plough
OSE RCM #:	2009-1366

CONTENTS

1 INTRODUCTION

This review is written in response to a request from the Division of Pulmonary and Allergy Products for assessment of labels and labeling for Dulera (Mometasone Furoate and Formoterol Fumarate Dihydrate) Inhalation Aerosol.

2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis[1] (FMEA) to evaluate the labels and labeling submitted as part of the May 21, 2009, submission (Appendix A thru E; no image of insert labeling).

3 RECOMMENDATIONS

Our evaluation noted areas where information on the label and labeling can be clarified and improved on to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 3.1 (*Comments to the Division)* for discussion during the review team's label and labeling meetings. Section 3.2 (*Comments to the Applicant)* contains our recommendations for the container labels, carton labeling, demonstrator label and carrying case. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have questions or need clarifications, please contact Carolyn Volpe, OSE Regulatory Project manager, at 301-796-5204.

3.1 COMMENTS TO THE DIVISION

Throughout the Highlights and Full Prescribing Information, the proprietary name Dulera is followed by the numerical portion of the strengths without the unit of measurement (mcg). Revise the presentation of the strengths to ensure the numerical portion of the product strength is followed by the unit of measurement (mcg) (b) (4)) throughout the insert labeling.

3.2 COMMENTS TO THE APPLICANT

A. Container Labels (Trade and Sample (b) (4), 100 mcg/5mcg, 200 mcg/5mcg)

1. Delete the strengths (XXX mcg/5 mcg) from the established name as this information will be duplicative. Revise the presentation of the proprietary name, established name and product strength to appear as follows:

   Dulera

   Mometasone furoate and formoterol fumarate dihydrate

   XX mcg/5 mcg

2. Add the statement "per actuation" to appear beside the product strength.
3. Delete or relocate to the side panel the statement: "See Package Insert for Full Prescribing Information" as this information is not needed on the principle display panel.

[1] Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

4. Increase the prominence of the statement: “Shake well before using” to ensure this essential information is not overlooked.

5. The product strengths all share the same overlapping blue font color even though the background colors are different. Revise the product strengths so that they are readily distinguishable and do not overlap to help minimize the risk of errors.

B. Carton Labeling (Trade and Sample (b) (4) ***, 100 mcg/5mcg, 200 mcg/5mcg)***

1. Delete the strengths (XXX mcg/5 mcg) from the established name as this information will be duplicative. Revise so that the presentation appears as follows:

   Dulera

   Mometasone furoate and formoterol fumarate dihydrate

   XX mcg/5 mcg

2. Add the unit of measurements (mcg) to the product strength throughout the labeling.

3. As currently presented, the green and blue graphics separates the strengths from the proprietary name and established names. Relocate the product strength on the principal display panel to appear immediately below the dosage form. Additionally, increase the prominence of the product strength.

4. Add the statement “per actuation” to appear beside the product strength.

5. The product strength appears on the left side panel without the proprietary name, established name and dosage form. Revise to include this information. Additionally, the proprietary name, established name and dosage form appear on the top flap without the product strength. Revise to include the product strength.

6. The product strengths all share the same overlapping blue font color even though the background colors are different. Revise the product strengths so that they are readily distinguishable and do not overlap to help minimize the risk of errors.

7. Relocate the statement: “Shake well before using” to the principal display panel and increase the prominence to ensure this information is not overlooked.

5 pages of Draft Carton and Container Labels have been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22518	ORIG-1	SCHERING CORP	MOMETASONE FUROATE/FORMOTEROL FUMARATE

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/s/

DEVEONNE G HAMILTON-STOKES
12/07/2009

TODD D BRIDGES
12/07/2009

KELLIE A TAYLOR
12/07/2009
on behalf of C Holquist

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Pulmonary and Allergy Products

Application Number: NDA 22-518

Name of Drug: Dulera (mometasone furoate/formoterol fumarate)

Applicant: Schering Plough

Material Reviewed:

Submission Date(s): May 21, 2009

Receipt Date(s): May 22, 2009

Submission Date of Structure Product Labeling (SPL): May 22, 2009

Type of Labeling Reviewed: PLR (SPL)

Background and Summary

This is the proposed PLR labeling which was submitted on May 21, 2009, received on May 22, 2009 by Schering Plough in their original New Drug Application for Dulera.

Review

The following issues/deficiencies with regard to format have been identified in the Highlights section of your proposed labeling.

Highlights Section:

1. Please check the spelling and/or wording for the indication in the Highlights section, in order to maintain consistency with the Full Prescribing Information. The current wording for the Indications and Usage in the Highlights section and Full Prescribing Information are as follows:

   Highlights: "(b) (4) treatment of asthma (b) (4) in patients 12 years of age and older."

Full Prescribing Information: "DULERA is indicated… [redacted] (b) (4) treatment of asthma, [redacted] (b) (4) in adults and children 12 years of age and older."

2. Please be more specific with your reference numbers:

   a. In the 1st bullet of the Contraindications section, change the reference number to 4 to 4.1.

   b. In the 2nd bullet of the Contraindications section, change the reference number from 4 to 4.2.

   c. Please provide a reference number for the Adverse Events section.

Recommendations

Address the identified deficiencies/issues and re-submit labeling by August 15, 2009. This updated version of labeling will be used for further labeling discussions.

_____
Eunice H. Chung, Pharm.D
Regulatory Project Manager

Supervisory Comment/Concurrence:

Sandy L. Barnes
Chief, Project Management Staff

Drafted: EC/22JULY2009
Revised/Initialed: 24JULY2009
Finalized: 28JULY2009
Filename: CSO Labeling Review Template (updated 1-16-07).doc

CSO LABELING REVIEW OF PLR FORMAT

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/s/

EUNICE H CHUNG
07/28/2009

DSI CONSULT: Request for Clinical Inspections

Date: July 16, 2009

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief (Acting), GCP2
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Susan Limb, MD, Medical Officer, Division of Pulmonary and Allergy Products (DPAP)
Sally Seymour, Associate Deputy Director for Safety, DPAP

From: *Eunice Chung, RPM, DPAP*

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 22-518
Applicant/ Applicant contact information (to include phone/email):

Susan Yule
Senior Manager and Liaison
Global Regulatory Affairs
Schering-Plough
O: (908) 740-7435
F: (908) 740-2243

Drug Proprietary Name: Mometasasone furoate/formoterol fumarate
NME or Original BLA (Yes/No): No
Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): Yes (age 12 years and above)
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): "the (b) (4) twice-daily (b) (4) treatment of asthma, (b) (4), in adults and children 12 years of age and older:

PDUFA: March 22, 2010
Inspection Summary Goal Date: January 19, 2010 (wrap-up meeting)

The proposed drug product is a novel HFA-227 pressurized metered-dose inhaler containing an inhaled corticosteroid/long-acting beta agonist (LABA) combination of mometasone furoate and formoterol fumurate (MF/F). MF/F is proposed for the (b) (4) twice-daily (b) (4) treatment of asthma, (b) (4) in adults and children 12 years of age and older. The proposed indication (b) (4) is a novel indication. (b) (4) dose levels are proposed: (b) (4) 100/5, and 200/5 mcg. The two monotherapy component drug substances have been previously approved as DPI formulations for the treatment of asthma.

II. Protocol/Site Identification

The Applicant's drug development program includes 4 efficacy and safety trials and 1 long-term safety trial. The 4 pivotal efficacy and safety trials were P04073, P04334, P04431, and P04705. We have chosen two US sites that enrolled patients in two of the phase 3 pivotal studies.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site #16 Nayak, Anjuli, MD Sneeze, Wheeze & Itch Associates, LLC 2010 Jacobssen Drive Normal, IL 61761 USA	P04334 P04073	21 20	Asthma
Site #12 Kerwin, Edward, MD Clinical Research Institute of Southern Oregon, PC 3860 Crater Lake Ave, Suite B Medford, OR 97504 USA	P04334 P04073	13 18	Asthma

III. Site Selection/Rationale

Study Sites 16 and 12 are the two top-enrolling US sites for two of the pivotal studies (P04334 and P04073) in the MF/F development program. Site 16 was the largest US site for both Study P04334 and P04073.

Domestic Inspections:

Reasons for inspections (please check all that apply):

__X__ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
____ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.

____ Other (specify):

IV. Tables of Specific Data to be Verified (if applicable)

Please verify the FEV1 primary efficacy variable and the key secondary efficacy variable, trough FEV1.

Should you require any additional information, please contact *Eunice Chung* at *301-796-4006 or Susan Limb* at 301-796-1951.

Concurrence: (as needed)

_____*X*_____ Medical Team Leader
_____*X* _____ Medical Reviewer

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/s/

Eunice Chung
7/16/2009 02:43:46 PM