

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22518Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22-518

SUPPL # N/A

HFD # 570

Trade Name Dulera

Generic Name mometasone furoate/formoterol fumarate

Applicant Name Schering Corporation (Merck)

Approval Date, If Known June 22, 2010

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(1)

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

YES NO

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

N/A

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

N/A

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES NO

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

NDA# 20-831	Foradil Aerolizer
NDA# 21-067	Asmanex Twisthaler
NDA# 21-592	Foradil Certihaler

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

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

-P04073,P04334, P04431, and P04139: Pivotal Phase 3 efficacy and safety trials,
-P04139:long-term safety trial
-C97-208 and C97-225:12-week, placebo-controlled dose-ranging trials,were reviewed for additional efficacy support of the MF 200 monocomponent
-Trial P4703, the dose counter study, was reviewed for support of the durability and reliability of the integrated dose counter device.
-Trial P04705, the non-inferiority trial comparing MF/F to a commercially marketed fluticasone/salmeterol combination (Advair), was reviewed briefly in terms of additional safety information but was not reviewed in detail for efficacy support. The other Phase 2 trials were reviewed primarily to support the dose selection of each monocomponent and to establish a clinical link to the related approved monotherapies, formoterol DPI (Foradil Aerolizer) and mometasone DPI (Asmanex Twisthaler).

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Investigation #1	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

- P04073,P04334, P04431, and P04139: Pivotal Phase 3 efficacy and safety trials,
- P04139:long-term safety trial
- C97-208 and C97-225:12-week, placebo-controlled dose-ranging trials,were reviewed for additional efficacy support of the MF 200 monocomponent
- Trial P4703, the dose counter study, was reviewed for support of the durability and reliability of the integrated dose counter device.
- Trial P04705, the non-inferiority trial comparing MF/F to a commercially marketed fluticasone/salmeterol combination (Advair), was reviewed briefly in terms of additional safety information but was not reviewed in detail for efficacy support. The other Phase 2 trials were reviewed primarily to support the dose selection of each monocomponent and to establish a clinical link to the related approved monotherapies, formoterol DPI (Foradil Aerolizer) and mometasone DPI (Asmanex Twisthaler).

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # 70,283 YES ! NO
! Explain:
Studies P04073, P04334, P04431, and P04139,
P04139, C97-208,C97-225, P4703, P04705 were all
sponsored by Schering

Investigation #2
IND # 70,283 YES ! NO
! Explain:
Studies P04073, P04334, P04431, and P04139,
P04139, C97-208,C97-225, P4703, P04705 were all
sponsored by Schering

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
YES ! NO
! Explain:
P05642, P05643,P05644 and P06144
were conducted and reported by
Novartis. There is a letter of
authorization from Novartis to use
these studies

Investigation #2
YES ! NO
! Explain:
P05642, P05643,P05644 and P06144
were conducted and reported by
Novartis. There is a letter of

authorization from Novartis to use these studies

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

YES NO

If yes, explain:

=====

Name of person completing form: Eunice Chung/Initialed: Sandy Barnes
Title: Regulatory Project Manager
Date: 6/4/2010

Name of Office/Division Director signing form: Badrul A. Chowdhury
Title: Director

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

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

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

/s/

EUNICE H CHUNG
06/22/2010

BADRUL A CHOWDHURY
06/22/2010

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

.DA/BLA#: 22-518 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: Pulmonary, Allergy, and Rheumatology Products PDUFA Goal Date: June 22, 2010 Stamp Date: 5/22/2010

Proprietary Name: Dulera

Established/Generic Name: mometasone furoate/formoterol fumarate

Dosage Form: Inhalation Aerosol (b) (4), 100/5 and 200/5 microgram,

Applicant/Sponsor: Schering Plough

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
- (2) _____
- (3) _____
- (4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s) 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: treatment of asthma in adults and children 12 years of age and older

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?
 Yes. Please proceed to Section D.
 No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?
 Yes. PREA does not apply. **Skip to signature block.**
 No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
 - No: Please check all that apply:
 - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups(Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: **(check, and attach a brief justification for the reason(s) selected)**

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	0 yr. __ mo.	4 yr. __ mo.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief**

justification):

* Not feasible:

 Necessary studies would be impossible or highly impracticable because:

- Disease/condition does not exist in children
- Too few children with disease/condition to study
- Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

 Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

 Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

∇ Justification attached.

or those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received	
<input type="checkbox"/> Neonate	_wk. _mo.	_wk. _mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input checked="" type="checkbox"/> Other	5 yr. _mo.	11 yr. _mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	_yr. _mo.	_yr. _mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	_yr. _mo.	_yr. _mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	_yr. _mo.	_yr. _mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

(b) (4)

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations)

Additional pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	12 yr. __ mo.	17 yr. __ mo.	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations)

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation? Yes. PREA does not apply. **Skip to signature block.** No. Please proceed to the next question.**Q2:** Is there a full waiver for all pediatric age groups for this indication (check one)? Yes: (Complete Section A.) No: Please check all that apply: Partial Waiver for selected pediatric subpopulations (Complete Sections B) Deferred for some or all pediatric subpopulations (Complete Sections C) Completed for some or all pediatric subpopulations (Complete Sections D) Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E) Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)Reason(s) for full waiver: **(check, and attach a brief justification for the reason(s) selected)** Necessary studies would be impossible or highly impracticable because: Disease/condition does not exist in children Too few children with disease/condition to study Other (e.g., patients geographically dispersed): _____ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients. Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling*) Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling*) Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*) Justification attached.*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived(fill in applicable criteria below)
 Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__wk. __mo.	__wk. __mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__yr. __mo.	__yr. __mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__yr. __mo.	__yr. __mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__yr. __mo.	__yr. __mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__yr. __mo.	__yr. __mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

Necessary studies would be impossible or highly impracticable because:

- Disease/condition does not exist in children
- Too few children with disease/condition to study
- Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__wk. __mo.	__wk. __mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__yr. __mo.	__yr. __mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__yr. __mo.	__yr. __mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__yr. __mo.	__yr. __mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__yr. __mo.	__yr. __mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__wk. __mo.	__wk. __mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__yr. __mo.	__yr. __mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__yr. __mo.	__yr. __mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__yr. __mo.	__yr. __mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__yr. __mo.	__yr. __mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__wk. __mo.	__wk. __mo.
<input type="checkbox"/>	Other	__yr. __mo.	__yr. __mo.
<input type="checkbox"/>	Other	__yr. __mo.	__yr. __mo.
<input type="checkbox"/>	Other	__yr. __mo.	__yr. __mo.
<input type="checkbox"/>	Other	__yr. __mo.	__yr. __mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	_wk. _mo.	_wk. _mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	_yr. _mo.	_yr. _mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	_yr. _mo.	_yr. _mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	_yr. _mo.	_yr. _mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	_yr. _mo.	_yr. _mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

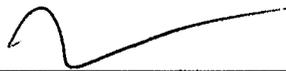
{See appended electronic signature page}

Regulatory Project Manager

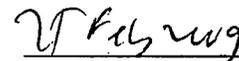
FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

Revised: 6/2008)

Schering Corporation 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. For persons providing services outside the United States, this certification does not apply, however assurance is given that ex-US service providers are reviewed to ensure they are qualified and otherwise acceptable.



Tom Haverly, M.D.
Group Vice President
Global Clinical Development
Schering-Plough Corporation



Date



ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 22-518 BLA #	NDA Supplement # 000 BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Dulera Established/Proper Name: mometasone furoate/formoterol fumarate Dosage Form: Inhalation		Applicant: Schering Plough Agent for Applicant (if applicable):
RPM: Eunice Chung		Division: Division of Pulmonary and Allergy Products
<p>NDA: NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(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). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p>
❖ User Fee Goal Date Action Goal Date (if different)		June 22, 2010
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input checked="" type="checkbox"/> CR
• Previous actions (<i>specify type and date for each action taken</i>)		<input checked="" type="checkbox"/> None
❖ Promotional Materials (<i>accelerated approvals only</i>) Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance www.fda.gov/cder/guidance/2197dft.pdf). If not submitted, explain _____		<input checked="" type="checkbox"/> Received

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application ² Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC Comments: _____	
❖ Date reviewed by PeRC (<i>required for approvals only</i>) If PeRC review not necessary, explain: _____	March 3, 2010
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)	<input type="checkbox"/> Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>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.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> 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) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [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). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [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). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> 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?

Yes No

(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).

- (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)?

Yes No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "**No**," continue with question (3).

- (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 (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

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

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

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

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

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) 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).</p> <p><i>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 section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist ³	6/22/2010
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) N/A
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	6/22/10;6/18/10; 6/7/2010;3/5/2010; 8/12/2009
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	5/22/2009
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> None

³ Fill in blanks with dates of reviews, letters, etc.
Version: 9/5/08

<ul style="list-style-type: none"> Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	6/22/10; 3/5/10
<ul style="list-style-type: none"> Original applicant-proposed labeling 	5/22/09
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date at upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> Most-recent division proposal for (only if generated after latest applicant submission) 	
<ul style="list-style-type: none"> Most recent applicant-proposed labeling 	6/18/2010; 3/5/2010; 5/22/2009
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input checked="" type="checkbox"/> RPM 5/12/10;7/28/09 <input checked="" type="checkbox"/> DMEDP 12/7/09 <input checked="" type="checkbox"/> DRISK 6/8/10 (medguide) <input checked="" type="checkbox"/> DDMAC 6/10/10; 6/3/10; 2/3/10 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
❖ Proprietary Name	
<ul style="list-style-type: none"> Review(s) (<i>indicate date(s)</i>) Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) 	6/4/10; 8/12/09; 8/4/09
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	1/15/10
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents www.fda.gov/ora/compliance_ref/aip_page.html	
<ul style="list-style-type: none"> Applicant in on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies	<input type="checkbox"/> None
<ul style="list-style-type: none"> Outgoing communications (<i>if located elsewhere in package, state where located</i>) 	In outgoing communication dated 5/26/10, 1/27/10
<ul style="list-style-type: none"> Incoming submissions/communications 	6/15/10; 6/11/10; 6/10/10
❖ Postmarketing Commitment (PMC) Studies	<input checked="" type="checkbox"/> None

⁴ Filing reviews for other disciplines should be filed behind the discipline tab.
Version: 9/5/08

<ul style="list-style-type: none"> Outgoing Agency request for postmarketing commitments (<i>if located elsewhere in package, state where located</i>) 	
<ul style="list-style-type: none"> Incoming submission documenting commitment 	
❖ Outgoing communications (<i>letters (except previous action letters), emails, faxes, telecons</i>)	6/21/10;6/18/10;6/16/10;6/15/10;6/11/10;6/10/10;6/8/10;6/4/10;5/26/10;5/18/10;5/17/10;5/7/10;2/26/10;2/24/10;2/19/10;2/18/10;1/27/10;1/19/10;12/23/09, 12/22/09, 10/26/09, 10/13/09, 08/4/09,7/20/09; 6/15/09;6/3/09
❖ Internal memoranda, telecons, etc.	6/22/10; 1/26/10
❖ Minutes of Meetings	
<ul style="list-style-type: none"> PeRC (<i>indicate date; approvals only</i>) 	<input type="checkbox"/> Not applicable 3/3/2010
<ul style="list-style-type: none"> Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) 	<input checked="" type="checkbox"/> Not applicable
<ul style="list-style-type: none"> Regulatory Briefing (<i>indicate date</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date</i>) 	<input type="checkbox"/> No mtg December 15, 2008
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> Other (e.g., EOP2a, CMC pilot programs) 	12/11/08;5/15/2008;2/28/08;11/30/04
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	N/A
<ul style="list-style-type: none"> 48-hour alert or minutes, if available 	N/A
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 6/22/10
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 6/22/10
Clinical Information⁵	
❖ Clinical Reviews	
<ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	See CDTL review
<ul style="list-style-type: none"> Clinical review(s) (<i>indicate date for each review</i>) 	5/19/2010;1/22/2010;7/14/2009
<ul style="list-style-type: none"> Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
❖ Safety update review(s) (<i>indicate location/date if incorporated into another review</i>)	In Clinical review, dated 1/22/2010
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	In Clinical review, dated 1/22/2010
❖ Clinical reviews from other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed

⁵ Filing reviews should be filed with the discipline reviews.
Version: 9/5/08

❖ Risk Management <ul style="list-style-type: none"> Review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) REMS Memo (<i>indicate date</i>) REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>) 	<input type="checkbox"/> None 6/22/10; 6/11/10;6/8/10;6/7/2010; 6/4/2010 2/18/2010 6/22/2010
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested 3/11/2010 1/27/2010; 12/14/2009
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 5/19/2010; 7/9/2009
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 5/14/2010; 1/22/2010; 7/28/09
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
<ul style="list-style-type: none"> ADP/T Review(s) (<i>indicate date for each review</i>) Supervisory Review(s) (<i>indicate date for each review</i>) Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None <input type="checkbox"/> None 2/25/2010 <input type="checkbox"/> None 6/10/10; 6/7/10; 5/12/10;1/19/10;7/7/09
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None requested
CMC/Quality <input type="checkbox"/> None	
❖ CMC/Quality Discipline Reviews	
<ul style="list-style-type: none"> ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>) Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>) CMC/product quality review(s) (<i>indicate date for each review</i>) BLAs only: Facility information review(s) (<i>indicate dates</i>) 	<input type="checkbox"/> None <input type="checkbox"/> None 5/26/2010 <input type="checkbox"/> None 6/14/10;3/15/2010; 1/22/2010;8/4/2009 <input type="checkbox"/> None
❖ Microbiology Reviews <ul style="list-style-type: none"> NDA: Microbiology reviews (sterility & pyrogenicity) (<i>indicate date of each</i>) 	December 1, 2009

<i>review)</i> <ul style="list-style-type: none"> • BLAs: Sterility assurance, product quality microbiology (<i>indicate date of each review</i>) 	<input type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (<i>indicate date of each review</i>)	<input type="checkbox"/> None 1/15/10;1/6/10 ;12/4/09
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	In CMC review dated 5/26/10
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ NDAs: Methods Validation	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed
❖ Facilities Review/Inspection	
<ul style="list-style-type: none"> • NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) 	Date completed: 03/22/2010 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<ul style="list-style-type: none"> • BLAs: <ul style="list-style-type: none"> ○ TBP-EER ○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) (<i>date completed must be within 60 days prior to AP</i>) 	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation Date completed: <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold

Appendix A to Action Package Checklist

An NDA or NDA supplemental 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) **Or** 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.
- (3) **Or** 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) **And** 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.
- (3) **And** 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) **Or** 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.
- (3) **Or** 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 ADRA.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22518	ORIG-2	SCHERING CORP	MOMETASONE FUROATE/FORMOTEROL FUMARATE
NDA-22518	ORIG-1	SCHERING CORP	MOMETASONE FUROATE/FORMOTEROL FUMARATE

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

/s/

EUNICE H CHUNG
06/22/2010

Memorandum

To: NDA# 22518, Dulera (mometasone furoate and formoterol fumarate)

From: Sally Seymour, MD
Deputy Director for Safety
Division of Pulmonary and Allergy Products

Regarding: Post-marketing Requirements and Commitment Templates

Date: June 22, 2010

New Drug Application (NDA) #22518 is for the combination product, mometasone furoate (MF) and formoterol fumarate (FF) inhalation aerosol in an HFA 227 metered dose inhaler (MDI) formulation. The indication is the treatment of asthma, including in adults and children 12 years of age and older. The tradename is Dulera Inhalation Aerosol. Two dosage strengths (ex-actuator) will be approved: 100 mcg mometasone furoate and 5mcg formoterol fumarate, and 200 mcg mometasone furoate and 5mcg formoterol fumarate.

Mometasone furoate and formoterol fumarate are currently approved active pharmaceutical ingredients in other inhalation products. Mometasone is a corticosteroid available in Asmanex Twisthaler for the treatment of asthma. Formoterol fumarate is a long acting beta agonist (LABA) available in Foradil Aerolizer, Foradil Certihaler, and in combination with budesonide as Symbicort Inhalation Aerosol. Inhaled corticosteroids (ICS) are one of the classes of medication used to treat asthma and are generally considered the most effective controller medication for asthma. LABA are another class of medications used for the treatment of bronchospasm in patients with asthma. The addition of a LABA to an ICS for the treatment of asthma is an accepted clinical practice and three ICS and LABA combination products are currently available: Advair Diskus, Advair HFA, and Symbicort Inhalation Aerosol.

LABA, including formoterol, have a known safety risk of asthma related death. Because of this risk, all LABA-containing products have a Boxed Warning and Risk Evaluation and Mitigation Strategy (Medication Guide and Communication Plan).

PREA is triggered for this application and pediatric studies in children 5 to < 12 years of age were deferred. Pediatric studies in children < 5 years of age were waived. The Applicant submitted a pediatric plan with multiple clinical trials. The proposed plan is generally acceptable, but detailed protocols will need to be reviewed once submitted. The pediatric trials will be post-marketing requirements.

The attached documents are the templates for the post-marketing requirements for Dulera.

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

PMR/PMC Description: Pediatric trial (b) (4): Long-term safety trial

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>7/31/2014</u>
	Study/Clinical trial Completion Date:	<u>10/31/2016</u>
	Final Report Submission Date:	<u>3/31/2017</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Safety and efficacy in patients 12 years of age and older are established.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Assess the long-term safety of mometasone furoate/formoterol (MF/F) in children 5 to 11 years of age.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

(b) (4)

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

PMR/PMC Description: Pediatric trial (b) (4): HPA axis assessment

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>5/31/2012</u>
	Study/Clinical trial Completion Date:	<u>10/31/2013</u>
	Final Report Submission Date:	<u>3/15/2014</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Safety and efficacy in patients 12 years of age and older are established.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Assess HPA axis effects of mometasone furoate/formoterol (MF/F) in children 5 to 11 years of age. In lieu of an HPA axis study, you may provide robust data to demonstrate that the systemic exposure of mometasone from DULERA is comparable or lower than that from the mometasone dry powder inhaler.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

(b) (4)

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

PMR/PMC Description: Pediatric trial P06476: Phamacodynamic evaluation with and without spacer

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>10/15/2010</u>
	Study/Clinical trial Completion Date:	<u>2/28/2012</u>
	Final Report Submission Date:	<u>7/31/2012</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Safety and efficacy in patients 12 years of age and older are established.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Evaluate the pharmacodynamic effect of mometasone furoate/formoterol (MF/F) in children 5 to 11 years of age with and without a spacer.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Randomized, single-dose, 4-period, cross-over trial in patients 5 to 11 years of age evaluating the pharmacodynamics of the following treatments: formoterol (F) DPI 12 mcg, mometasone/formoterol (MF/F) MDI 100/10 mcg with and without a spacer, placebo with and without a spacer.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

PMR/PMC Description: Pediatric trial ^{(b) (4)}: Mometasone furoate (MF) dose-ranging

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>4/15/2012</u>
	Study/Clinical trial Completion Date:	<u>3/31/2014</u>
	Final Report Submission Date:	<u>8/31/2014</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Safety and efficacy in patients 12 years of age and older are established.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Assess the efficacy and safety of mometasone furoate MDI in children 5 to 11 years of age.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

(b) (4)

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

PMR/PMC Description: Pediatric trial (b) (4): Efficacy and safety of mometasone furoate/formoterol

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>5/31/2014</u>
	Study/Clinical trial Completion Date:	<u>8/31/2014</u>
	Final Report Submission Date:	<u>1/31/2017</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Safety and efficacy in patients 12 years of age and older are established.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Assess the efficacy and safety of mometasone furoate/formoterol (MF/F) in children 5 to 11 years of age.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

(b) (4)

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
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 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
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PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

PMR/PMC Description: Pediatric trial (b) (4): Pharmacokinetics with and without spacer

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>7/31/2012</u>
	Study/Clinical trial Completion Date:	<u>6/30/2014</u>
	Final Report Submission Date:	<u>11/15/2014</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Safety and efficacy in patients 12 years of age and older are established.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Assess pharmacokinetics of mometasone furoate/formoterol (MF/F) in children 5 to 11 years of age.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

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- Assess signals of serious risk related to the use of the drug?
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- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
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4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

(b) (4)

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
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 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
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 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
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 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
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- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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/

SALLY M SEYMOUR

06/22/2010



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

FACSIMILE TRANSMITTAL SHEET

DATE: June 21, 2010

To: Mike Belman	From: Eunice Chung
Company: Schering-Plough	Division of Pulmonary and Allergy Drug Products
Fax number: Secure email	Fax number: 301-796-9728
Phone number: N/A	Phone number: 301-796-2300

Subject: NDA 22518 Information Request

Total no. of pages including cover:

Comments: Please respond by June 22, 2010

Document to be mailed: YES xNO

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Your NDA submission, NDA 22-518, is currently under review. We have the following request for information:

For P04334 and P04431, provide subject ID numbers, case narratives, and CRFs for the patients who qualified per protocol as a severe asthma exacerbation (clinically judged deterioration in asthma or reduction in lung function) by hospitalization or receipt of emergency treatment.

Please submit a response via email to Eunice.Chung@fda.hhs.gov by June 22, 2010. The official response should be submitted to the NDA shortly after as well. If you have any questions, please contact Eunice Chung, Regulatory Project Manager, at 301-796-4006.

Drafted by: SLimb/21JUN2010
Initialied by: SSeymour/21JUN2010
SBarnes/21JUN2010

Finalized by: Echung/21JUN2010

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22518

ORIG-1

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/s/

EUNICE H CHUNG

06/21/2010



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

FACSIMILE TRANSMITTAL SHEET

DATE: June 21, 2010

To: Mike Belman	Eunice Chung
Company: Schering-Plough	From: Division of Pulmonary and Allergy Drug Products
Fax number: Secure email	Fax number: 301-796-9728
Phone number: N/A	Phone number: 301-796-4006

Subject: **NDA 22518 Information Request DUE ASAP**

Total no. of pages including
cover:

Comments:

Document to be mailed: YES xNO

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Your REMS proposal, submitted via email on June 17, 2010, is currently under review. We may have additional comments. We have the following request for information:

1. The background portion of the document refers only to the February 18, 2010, safety communication and does not include the update from June 2, 2010, which is more consistent with the recommended LABA class label changes. This section has been revised to reflect the most recent update from June 2, 2010.
2. The printed/web materials link to the February 18, 2010, safety communication but the language reflects the June 2, 2010, update. Provide the link to the June 2, 2010, more prominently in relationship to this information.

Please submit a response via email (track change document and clean version) by 11A.M. on Tuesday, June 22, 2010, to Eunice.Chung@fda.hhs.gov. The official response should be submitted to the NDA shortly after as well. If you have any questions, please contact Eunice Chung, Regulatory Project Manager, at 301-796-4006.

Enclosure: REMS document

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immediately following this page

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22518

ORIG-1

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/s/

EUNICE H CHUNG

06/21/2010



**Food and Drug Administration
Center for Drug Evaluation and Research**

OFFICE OF DRUG EVALUATION II

FACSIMILE TRANSMITTAL SHEET

DATE: June 18, 2010

To: Mike Belman	From: Eunice Chung
Company: Schering-Plough	Division of Pulmonary and Allergy Drug Products
Fax number: Secure email	Fax number: 301-796-9728
Phone number: N/A	Phone number: 301-796-4006
Subject: NDA 22518 Labeling Comments	

Total no. of pages including cover:

Comments: Please provide a response no later than June 21, 2010

Document to be mailed: YES XNO

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We are currently reviewing your Package Insert and Medication Guide for NDA 22-518 for Dulera, submitted via email on June 18, 2010 and June 14, 2010, respectively. We have the following comments in track change format. We may have additional comments as our review proceeds. Please provide a response no later than June 21, 2010 via email to **Eunice.Chung@fda.hhs.gov**. Your response will also have to be submitted to the NDA shortly thereafter. If you have any questions, please contact Eunice Chung, Regulatory Project Manager, at 301-796-4006.

Enclosure: Package Insert
 Medication Guide

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
06/18/2010



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

FACSIMILE TRANSMITTAL SHEET

DATE: June 18, 2010

To: Mike Belman	Eunice Chung
Company: Schering-Plough	From: Division of Pulmonary and Allergy Drug Products
Fax number: Secure email	Fax number: 301-796-9728
Phone number: N/A	Phone number: 301-796-4006

Subject: NDA 22518 Information Request DUE ASAP or Monday, June 21, 2010

Total no. of pages including cover:

Comments:

Document to be mailed: YES xNO

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Your REMS proposal, submitted via email on June 17, 2010, is currently under review. We may have additional comments. We have the following request for information.

1. See the attached REMS with a few track changes.

Goals:

Your proposed revisions of the goals for the Dulera REMS are acceptable.

Communication Plan:

1. DHCPL:

- a. Your plan for the distribution (within 60 days of the product approval then at 6 months) of the DHCPL is acceptable.
- b. Your revisions of the new prescribing guidelines, as per DPARP's recommendations (June 15, 2010 FDA comments) are acceptable. We refer you to our track changes in the DHCPL.
- c. Your revision of the boxed warning in the DHCPL and in the medical society letter per DPARP's recommendations (June 15, 2010 FDA comments) is noted and acceptable, except we ask that you add *"See full prescribing information for complete boxed warning"*.

2. Printed or web-based educational materials

- a. Refer to our track changes in the Printed / Web-based Information letter.
- b. Your proposal for the posting of the Dulera printed or web-based information on the Merck website within 10 days of product approval and making web-based materials available for 3 years is acceptable.
- c. Your proposal to include, at a minimum the following, in the content of the Dulera print or web-based material is acceptable:
 - i. Information about the risk
 - ii. Key data regarding the risk (e.g. SMART, SNS)
 - iii. New prescribing guidelines
 - iv. Currently available LABAs and approved uses
 - v. Prescribing information for DULERA
 - vi. Patient Counseling Information
 - vii. Medication Guide for DULERA
 - viii. Questions and Answers
 - ix. DHCP letter (for a period of 1 year)

3. Professional societies:

Your proposal to:

- a. Communicate (via a letter) with the leadership of the various professional societies is acceptable. The list of the professional societies that you intend to target is acceptable.
- b. Request the targeted professional societies to disseminate to their members the Dulera safety information/new prescribing guidelines is acceptable.
- c. Submission of the total number of recipients of the Dulera information prior to product launch is acceptable.

Supporting Document:

1. Your revision of the REMS assessment plan in the Supporting document is acceptable with the exception of the following:
 - a. Since the MG will be dispensed with each Dulera prescription / unit of use, remove the following two bullets regarding the MG dispensing from your REMS assessment plan in the Supporting Document (under 5.a. iii. and iv.):
 - A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
 - A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance
 - b. Delete the 4th bullet under the Section 2, Background, third paragraph:

(b) (4)

REMS Document:

Refer to our track changes in the REMS document.

Please submit a response via email by noon on Monday, June 21, 2010, to Eunice.Chung@fda.hhs.gov. The official response should be submitted to the NDA shortly after as well. If you have any questions, please contact Eunice Chung, Regulatory Project Manager, at 301-796-4006.

26 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Drafted by: EChung/18JUN2010

Initialed by: SLimb/18JUN2010
SSeymour/18JUN2010
SBarnes/18JUN2010

Finalized by: EChung/18JUN2010

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22518

ORIG-1

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/s/

EUNICE H CHUNG

06/18/2010



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

FACSIMILE TRANSMITTAL SHEET

DATE: June 16, 2010

To: Mike Belman	Eunice Chung, RPM
Company: Schering-Plough	From: Division of Pulmonary and Allergy Drug Products
Fax number: Secure E-mail	Fax number: 301-796-9728
Phone number: N/A	Phone number: 301-796-4006

Subject: CMC Information Request

Total no. of pages including cover:

Comments:

Document to be mailed: YES xNO

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Your submission dated March 5, 2010, to NDA 22-518, is currently under review. We have the following request for information:

Carton and Container:

1. The white text on the purple background of the 200 mcg/5 mcg strength provides a poor contrast. Revise the text color or background color to improve readability.
2. The strength's appearing on the container/carton labeling twice is duplicative and unnecessary. Delete the strength that separates the established name from the dosage form on the container label and carton labeling. Additionally, on the container label relocate the color bar and strength to appear below the dosage form. Adequate spacing and room could be allowed by moving the Trade name, established name and dosage form up near the top of the container label. Thus, the presentation would be as follows:

Dulera

(Mometasone furoate and formoterol fumarate dihydrate)

Inhalation Aerosol

XX mcg/5 mcg

Please submit your response by Thursday, June 17, 2010. If you have any questions, please contact Eunice Chung, Regulatory Project Manager, at 301-796-4006.

NDA #22-518

Drafted by: EChung/16JUN2010
Initialed by: ASchroeder/16JUN2010
PPeri/16JUN2010
SBarnes/16JUN2010

Finalized by: EChung/16JUN2010

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22518

ORIG-1

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/s/

EUNICE H CHUNG

06/16/2010



**Food and Drug Administration
Center for Drug Evaluation and Research**

OFFICE OF DRUG EVALUATION II

FACSIMILE TRANSMITTAL SHEET

DATE: June 15, 2010

To: Mike Belman	From: Eunice Chung
Company: Schering-Plough	Division of Pulmonary and Allergy Drug Products
Fax number: Secure email	Fax number: 301-796-9728
Phone number: N/A	Phone number: 301-796-4006
Subject: NDA 22518 Labeling Comments	

Total no. of pages including cover:

Comments:

Document to be mailed: YES XNO

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We are currently reviewing your Package Insert, Medication Guide and REMS for NDA 22-518 for Dulera, submitted via email on June 7, 2010, June 14, 2010, and June 9, 2010, respectively. We may have additional comments as our review proceeds. Submit a revised labeling, medication guide, and REMS proposal incorporating these comments no later than June 17, 2010.

The following comments are in reference to the proposed package insert:

1. Highlights, Adverse Reactions: Amend the adverse reactions to reflect treatment-emergent adverse events, not treatment-related.
2. Section 6.1, Adverse Reactions, Clinical Trials Experience: Treatment-emergent adverse events from P04334 and P04431 should be reported in this section, not treatment-related. Provide the correct adverse reactions, values, and justification for the numbers reported.
3. Section 8.5, Geriatric Use: Provide the number of patients 75 years of age and older in P04334, P04431, and P04139.
4. Section 14, Clinical Studies: The labels for Figure 1 obscure the line curves. Revise the figure so that the curves are clearly marked. Figure 2 has been removed since the primary objective of P04431 (Trial 2) was the justification for two dose levels of DULERA, which is reflected in the trough FEV1 values.
5. Section 14, Clinical Studies, Tables 4 and 7: The 6th criterion in the table for a clinically judged deterioration in asthma or reduction in lung function is treatment with additional asthma medications. Specify the number of patients in each treatment group who met this criterion due to treatment with a non-corticosteroid medication and specify the medication that was administered. Provide this information separately from the revised label.
6. Section 14, Clinical Studies, Table 5: As the proposed changes do not change the conclusions, the p-values have been amended to correspond with the p-values reported in the original study reports.
7. Section 14, Clinical Studies: We have revised the AQLQ section to include the analysis using the average imputation method. This method of imputation is preferred over the LOCF. You propose to include the AQLQ data using the LOCF imputation method; however, your pre-specified analysis plan specified the analysis of the AQLQ data at week 26 and did not specify the LOCF method of imputation.

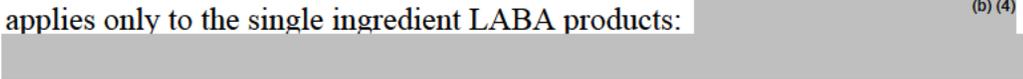
General Comments (format):

8. When referencing other sections of the label, provide the references in a consistent, italicized font in brackets, e.g. [*see Warnings and Precautions (5.1)*]. Do not use all upper-case letters.
9. Highlights Section: 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.”
10. Table of Contents: Remove periods after numbers for section headings in the Table of Contents Section.
11. Table of Contents: The same title for the boxed warning that appears in the Highlights and Full Prescribing 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.
12. Full Prescribing Information: Add the following statement at the end of the Table of Contents: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
13. Full Prescribing Information: Remove periods after numbers for all section headings.

The following comment is in reference to the proposed Medication Guide:

14. Revise the subsection titled, “The most common side effects of DULERA include,” to list the most common treatment-emergent adverse reactions, not treatment-related, that occurred more commonly than placebo. Maintain consistency with the Highlights and Section 6.1 of the package insert.

The following comments are in reference to the proposed REMS:

15. Include in the DHCPL that Dulera has a risk evaluation and a mitigation strategy (REMS) that consists of a Medication Guide and a communication program.
16. Include in the DHCPL in the new prescribing guidelines the following: *DULERA should only be used for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA.*
17. Omit the following from the DHCPL in the new prescribing guidelines as this applies only to the single ingredient LABA products: (b) (4)


Please provide a response by June 17, 2010 via email to [**Eunice.Chung@fda.hhs.gov**](mailto:Eunice.Chung@fda.hhs.gov). Your response will also have to be submitted to the NDA shortly thereafter. If you have any questions, please contact Eunice Chung, Regulatory Project Manager, at 301-796-4006.

Enclosure: Package Insert
 Medication Guide

30 pages of Draft Labeling 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

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/s/

EUNICE H CHUNG

06/15/2010



Schering-Plough Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033-0530 USA
T +1 908 298 4000
www.schering-plough.com

June 15, 2010

Badrul Chowdhury, MD, PhD, Director
Division of Pulmonary and Allergy Products
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20857

NDA 22-518
DULERA®; SCH 418131
**(mometasone furoate/
formoterol fumarate)**
INHALATION AEROSOL

SUBJECT: GENERAL CORRESPONDENCE

Dear Dr. Chowdhury,

Enclosed please find a response to Dr. Eunice Chung's email request for pediatric study timeline revisions that specify the month and year. The revisions were requested in response to the revised pediatric plan submitted to the NDA 11 June 2010. This amendment submits to the IND the formal response that has been supplied via email to Dr. Chung 11 June 2010.

Pediatric study timelines:



Should you require any further information regarding this submission, please contact me at (908) 740-4997/michael.belman@merck.com or David De Sousa at (908) 740-4285/david.desousa@merck.com.

This submission is provided in electronic format as per the ICH M2: Electronic Technical Document Specification. Please see the Electronic Information form enclosed behind the cover letter.

Please be advised that the material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j) as well as the FDA regulations.

Sincerely,



Michael Belman
Director & Liaison
Global Regulatory Affairs

MB:dp

Electronic Submission Information

Description Format (Electronic)

The following identifies the primary sections included in this submission. The below table provides details of the individual modules.

Module	Description	Electronic
	XML	X
1	US REGIONAL ADMINISTRATIVE INFORMATION	X

Electronic Submission Summary

File Formats:

Extensible Markup Language (XML)
Portable Document Format (PDF)

Total Size:

Electronic Submission - 416 KB

Virus Verification:

This is to certify that this electronic submission has been scanned for viruses using McAfee Virus Scan, version 8.0i.

Sponsor Contact:

Global Regulatory Affairs:

Mike Belman
Director and Liaison
Global Regulatory Affairs
(908) 740-4997
michael.belman@spcorp.com

Technical Support:

Deborah Lahr
Senior Manager
Global Regulatory Affairs
(908) 740-5436
deborah.lahr@spcorp.com



Schering-Plough Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033-0530 USA
T +1 908 298 4000
www.schering-plough.com

June 11, 2010

Badrul Chowdhury, MD, PhD, Director
Division of Pulmonary and Allergy Products
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20857

NDA 22-518
DULERA®; SCH 418131
**(mometasone furoate/
formoterol fumarate)**
INHALATION AEROSOL

SUBJECT: RESPONSE TO FDA REQUEST FOR INFORMATION

Dear Dr. Chowdhury,

Enclosed please find the updated pediatric development plan in response to Dr. Eunice Chung's FAX request dated 07 May 2010. This amendment submits to the IND the formal response that has been supplied via email to Dr. Chung 11 June 2010.

Should you require any further information regarding this submission, please contact me at (908) 740-4997/michael.belman@merck.com or David De Sousa at (908) 740-4285/david.desousa@merck.com.

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Sincerely,

Michael Belman
Director & Liaison
Global Regulatory Affairs

MB:cp

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Module	Description	Electronic
	XML	X
1	US REGIONAL ADMINISTRATIVE INFORMATION	X

Electronic Submission Summary

File Formats: Extensible Markup Language (XML)
Portable Document Format (PDF)

Total Size: Electronic Submission - 600 KB

Virus Verification: This is to certify that this electronic submission has been scanned for viruses using McAfee Virus Scan, version 8.0i.

Sponsor Contact:

Global Regulatory Affairs: Mike Belman
Director and Liaison
Global Regulatory Affairs
(908) 740-4997
michael.belman@spcorp.com

Technical Support: Deborah Lahr
Senior Manager
Global Regulatory Affairs
(908) 740-5436
deborah.lahr@spcorp.com



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

FACSIMILE TRANSMITTAL SHEET

DATE: June 11, 2010

To: Mike Belman	Eunice Chung
Company: Schering-Plough	From: Division of Pulmonary and Allergy Drug Products
Fax number: Secure email	Fax number: 301-796-9728
Phone number: N/A	Phone number: 301-796-4006

Subject: **NDA 22518 Information Request DUE ASAP**

Total no. of pages including
cover:

Comments:

Document to be mailed: YES xNO

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Your NDA submission, NDA 22-518, dated June 10, 2010, is currently under review. We have the following request for information.

1. See the appended Dulera REMS proposal (Appendix A) for tracked changes corresponding to comments in this review.

2. REMS Goals:

The first three goals of your REMS are acceptable, however since the communication plan is not targeted to patients, the only source of information that patients will be receiving is the Medication Guide which is specific to your product.

Revise your 4th goal as follows:

To inform patients of the other serious risks associate with the use of Dulera

3. Medication Guide:

We have no additional comments on the Medication Guide at this time. See the appended REMS for editorial comments on this section of the REMS.

4. Communication Plan:

a. Your proposed website materials are not sufficient. Your communication plan must include printed or preferably web-based material that includes information on the risk of serious asthma outcomes and the safe use of LABAs and will be required to be posted or provided for a period of at least 3 years following the approval of the REMS. The content of the print or web-based material must include at a minimum include the following:

- i. Information about the risk
- ii. Key data regarding the risk (e.g. SMART, SNS)
- iii. New prescribing guidelines
- iv. Currently available LABAs and approved uses
- v. Prescribing information for Dulera
- vi. Patient Counseling Information
- vii. Medication Guide for Dulera
- viii. Questions and Answers
- ix. DHCP Letter (for a period of 1 year)

Some optional pieces could include:

- Resource list of future meetings and peer reviewed journal articles related to LABAs
- Links to FDA Alert(s) for the LABAs

- b. Submit a letter for review that is to be directed to the leadership of the professional societies. You may consider the ESA letters to the professional societies as an example when drafting these letters. You can find the Aranesp or Epogen REMS on the FDA website. In addition to the letter, your communication to the professional societies must include a link to the website or if hard copies of the pre-printed materials (see above).
- c. We have no additional comments on your DHCP letter at this time, however additional comments may follow. The DHCP letter should be also be available on your website for a period of 1 year after approval of the REMS.
- d. The communication plan materials including the website presentation, the DHCP, and the communication materials to professionals' societies must be submitted for review ASAP. These materials are part of the final approved REMS.

5. **Timetable for Submission of Assessments:** Your timetable for submission of assessments is acceptable. Please see the appended REMS for editorial comments to this section of the REMS.

6. REMS Assessments Plan:

- a. You have eliminated elements of your REMS Assessment Plan previously agreed upon. Since your REMS includes a communication plan to HCPs, you will need to assess whether your communication plan has been effective in assessing the goals of your REMS: Your REMS Assessment Plan will include at minimum the following information:
 - i. An evaluation of patients' understanding of the serious risks of Dulera (mometasone furoate and formoterol fumarate) Inhalation Aerosol, including the increased risk of asthma-related deaths.
 - ii. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
 - iii. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance
 - iv. An analysis of prescribers' understanding of the increased risk of asthma related deaths and the safe use of LABAs
 - v. .A description of specific measures that would be taken to increase awareness if the assessment of healthcare prescribers indicates that prescriber awareness is not adequate.
 - vi. A narrative summary with analysis of all reported asthma-related deaths during the reporting period.

- vii. Drug use patterns (reasons for use, patient demographics, length of therapy, prescribing medical specialties)
 - viii. With regard to the communication plan:
 - 1. The date of launch of the communication plan (DHCP letter, website, and communication to professional societies)
 - 2. The number of recipients of the DHCP letter distribution
 - 3. Date(s) of distribution of the DHCP letter
 - 4. A copy of all documents included in each distribution
 - 5. The professional societies that you communicated to
 - 6. The information that the professional societies disseminated to its members and the timing for the dissemination
 - ix. Based on the information reported, an assessment of and conclusion regarding whether the REMS is meeting its goal and whether modifications to the REMS are needed.
- b. We acknowledge your comment to submit your survey methodology 90 days prior to the evaluation of patients understanding of the risks and safe use of Dulera. You should also submit your prescriber survey 90 days prior to your evaluation of prescribers' knowledge and understanding of the risks and safe use of LABAs.

7. General comments:

- Submit your proposed REMS and other materials in WORD format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS and appended materials be a single WORD document. All REMS materials should be free of promotional language and tone.
- Consider these comments interim comments. You will receive additional comments on your proposed REMS, REMS materials, and REMS supporting document as we continue our review of the application.

Please submit a response via email as soon as possible, to Eunice.Chung@fda.hhs.gov. The official response should be submitted to the NDA shortly after as well. If you have any questions, please contact Eunice Chung, Regulatory Project Manager, at 301-796-4006.

Application
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Submitter Name

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NDA-22518

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/s/

EUNICE H CHUNG

06/11/2010



NDA 22-518

METHODS VALIDATION MATERIALS RECEIVED

Schering-Plough
Attention: Greg Howe
Senior Manager and Liaison
Global Regulatory Affairs-CMC
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Dr. Howe:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dulera (mometasone furoate and formoterol fumarate) Inhalation Aerosol, [REDACTED] (b) (4) mometasone furoate 100 mcg and formoterol fumarate dihydrate 5 mcg inhalation aerosol and to our April 10 2010 letter requesting sample materials for methods validation testing.

We acknowledge receipt on June 11, 2010 of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

James F. Allgire
Team Leader
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

JAMES F ALLGIRE

06/11/2010



Schering-Plough Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033-0530 USA
T +1 908 298 4000
www.schering-plough.com

June 10, 2010

Badrul Chowdhury, MD, PhD, Director
Division of Pulmonary and Allergy Products
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20857

NDA 22-518
DULERA®; SCH 418131
**(mometasone furoate/
formoterol fumarate)**
INHALATION AEROSOL

SUBJECT: RESPONSE TO FDA REQUEST FOR INFORMATION

Dear Dr. Chowdhury,

This amendment submits to the IND a statement of agreement that was supplied via email to Dr. Eunice Chung June 2, 2010. The sponsor agrees to work with FDA to develop a mutually acceptable protocol for a post marketing study to evaluate the (b) (4) and hereby affirm our intent to conduct an agreed study.

The agreement was provided in response to a post-marketing FAX dated May 26, 2010. The post-marketing study was initially discussed on May 20, 2010 in a teleconference with the Agency.

Should you require any further information regarding this submission, please contact me at (908) 740-4997/michael.belman@merck.com or David De Sousa at (908) 740-4285/david.desousa@merck.com.

This submission is provided in electronic format as per the ICH M2: Electronic Technical Document Specification. Please see the Electronic Information form enclosed behind the cover letter.

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Sincerely,

Michael Belman
Director & Liaison
Global Regulatory Affairs

MB:cp

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Extensible Markup Language (XML)
Portable Document Format (PDF)

Total Size:

Electronic Submission - 376 KB

Virus Verification:

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Sponsor Contact:

Global Regulatory Affairs:

Mike Belman
Director and Liaison
Global Regulatory Affairs
(908) 740-4997
michael.belman@spcorp.com

Technical Support:

Deborah Lahr
Senior Manager
Global Regulatory Affairs
(908) 740-5436
deborah.lahr@spcorp.com



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

FACSIMILE TRANSMITTAL SHEET

DATE: June 10, 2010

To: Mike Belman	From: Eunice Chung, RPM
Company: Schering-Plough	Division of Pulmonary and Allergy Drug Products
Fax number: Secure E-mail	Fax number: 301-796-9728
Phone number: N/A	Phone number: 301-796-4006

Subject: Nonclinical Information Request

Total no. of pages including cover:

Comments: Please provide a response to the request ASAP

Document to be mailed: YES xNO

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Your response via email, dated June 9, 2010, to our information request dated June 8, 2010, is currently under review and we have the following comments:



Please provide a response by COB June 10, 2010 via email to Eunice.Chung@fda.hhs.gov. Your response will also have to be submitted to the NDA shortly thereafter. If you have any questions, please contact Eunice Chung, Regulatory Project Manager, at 301-796-4006.



NDA #22-518

Drafted by: Tim Robison/9JUN2010
Initialed by: Molly Shea/9JUN2010
SBarnes/10JUN2010

Finalized by: EChung/10JUN2010

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22518

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/s/

EUNICE H CHUNG

06/10/2010

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

Memorandum

Date: June 10, 2010

To: Eunice Chung -- Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
(DPARP)

From: Robyn Tyler, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: NDA #22-518
DDMAC labeling comments for DULERA® 100/5 mcg and
200/5 mcg Inhalation Aerosol

DDMAC has reviewed the proposed Medication Guide (MG) submitted for consult on April 30, 2010. The comments are based on the version sent to the DDMAC project manger via email on June 7, 2010.

DDMAC offers the following comments.

33 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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Product Name

NDA-22518

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/s/

ROBYN C TYLER

06/10/2010



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

FACSIMILE TRANSMITTAL SHEET

DATE: June 9, 2010

To: Mike Belman	Eunice Chung
Company: Schering-Plough	From: Division of Pulmonary and Allergy Drug Products
Fax number: Secure email	Fax number: 301-796-9728
Phone number: N/A	Phone number: 301-796-2300

Subject: **NDA 22518 Information Request DUE June 10, 2010**

Total no. of pages including
cover:

Comments:

Document to be mailed: YES xNO

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The revised labeling submitted via email on June 8, 2010, included the following information on the AQLQ:

(b) (4)

According to the complete study report for Study P04334, the pre-specified endpoint was the change from baseline to Week 26, which yields a crude treatment difference of 0.25, not 0.5 (Table 16, CSR P04334). Clarify how the value of 0.5 featured in the revised label is derived.

Please submit a response via email by COB June 10, 2010, to Eunice.Chung@fda.hhs.gov. The official response should be submitted to the NDA shortly after as well. If you have any questions, please contact Eunice Chung, Regulatory Project Manager, at 301-796-4006.

Drafted by: EChung/9JUN2010

Initialed by: SLimb/9JUN2010
SSeymour/9JUN2010
SBarnes/9JUN2010

Application
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Submission
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Product Name

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ORIG-1

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/s/

EUNICE H CHUNG

06/09/2010



Food and Drug Administration
Center for Drug Evaluation and Research
OFFICE OF DRUG EVALUATION II

FACSIMILE TRANSMITTAL SHEET

DATE: June 9, 2010

To: Mike Belman	From: Eunice Chung
Company: Schering-Plough	Division of Pulmonary and Allergy Drug Products
Fax number: Secure email	Fax number: 301-796-9728
Phone number: N/A	Phone number: 301-796-4006
Subject: NDA 22518 Medication Guide Comments	

Total no. of pages including cover:

Comments:

Document to be mailed: YES XNO

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Your revised Medication Guide, dated March 5, 2010, is currently under review. The following comments refer to the Patient Instructions for Use:

1. Include a color picture of the actual colors on the device, since the text refers specifically to a “blue” plastic actuator.
2. An enlarged image of the counter has been added to illustrate appropriate reading of the dose counter.

Please submit a response via email by COB June 14, 2010, to Eunice.Chung@fda.hhs.gov. The official response should be submitted to the NDA shortly after as well. If you have any questions, please contact Eunice Chung, Regulatory Project Manager, at 301-796-4006.

Drafted by: Echung/9JUN2010
Initialed by: SBarnes/9JUN2010
Slimb/9JUN2010
SSeymour/9JUN2010

Finalized by: EChung/9JUN2010

15 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

EUNICE H CHUNG

06/09/2010



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

FACSIMILE TRANSMITTAL SHEET

DATE: June 8, 2010

To: Mike Belman	From: Eunice Chung, RPM
Company: Schering-Plough	Division of Pulmonary and Allergy Drug Products
Fax number: Secure E-mail	Fax number: 301-796-9728
Phone number: N/A	Phone number: 301-796-4006

Subject: Nonclinical Information Request

Total no. of pages including cover:

Comments: Please provide a response to the request ASAP

Document to be mailed: YES xNO

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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 [REDACTED] (b) (4)
[REDACTED] refer to
and how were these numbers obtained.

b. Clarify the statement that [REDACTED] (b) (4)
[REDACTED] 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.

[REDACTED] (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Please provide a response by June 10, 2010 via email to Eunice.Chung@fda.hhs.gov. Your response will also have to be submitted to the NDA shortly thereafter. If you have any questions, please contact Eunice Chung, Regulatory Project Manager, at 301-796-4006.

NDA #22-518

Drafted by: Tim Robison/7JUN2010
Initialed by: Molly Shea/7JUN2010
SBarnes/8JUN2010

Finalized by: EChung/8JUN2010

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

06/08/2010

MEMORANDUM

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

TO: Dulera (mometasone furoate/formoterol fumarate) Inhalation Aerosol NDA 22-518
Department of Pulmonary and Allergy Products

THROUGH: Suzanne Barone, Ph.D. Team Leader
Compliance Risk Management and Strategic Problem Solving Team
Division of Compliance Risk Management and Surveillance
Office of Compliance

FROM: Michelle Marsh, Consumer Safety Officer
Compliance Risk Management and Strategic Problem Solving Team
Division of Compliance Risk Management and Surveillance
Office of Compliance, CDER

SUBJECT: OC review of proposed REMS submitted 3/5/2010 by Schering Plough

This memorandum provides comments and recommendations from the CDER Office of Compliance (OC) on the proposed REMS submitted 3/5/2010 by Schering Plough for Dulera (mometasone furoate/formoterol fumarate) Inhalation Aerosol NDA 22-518. The proposed REMS consists of a Medication Guide, Communication Plan, and Timetable for Submission of Assessments.

BACKGROUND

Based on information obtained from the Salmeterol Multi-Center Asthma Research Trial (SMART) and clinical trial data presented as a meta-analysis at the December 10-11, 2008, joint meeting of the Pulmonary Allergy Drugs, Drug Safety and Risk Management, and Pediatric Advisory Committees, and the discussion at the joint Advisory Committee meeting, the FDA determined that a REMS is necessary to ensure that the benefits of Dulera (mometasone furoate/ formoterol fumarate) Inhalation Aerosol outweigh the risks of serious asthma outcomes (asthma related death, intubations, and hospitalizations) associated with the use of the class of long acting beta agonists (LABAs).

The proposed REMS submitted by Schering Plough dated 3/5/2010 consist of:

1. Medication Guide
2. Communication Plan
 - a. Dear Healthcare Provider Letter
 - b. Website
3. Timetable for Submission of Assessments

OC COMMENTS

1. The Medication Guide section of the REMS is acceptable.
2. The language in the Timetable for Submission of Assessments in the REMS is acceptable.

OC RECOMMENDATIONS

The following recommendations were included in the OSE DRISK Dulera REMS Interim Review comments dated 6-4-2010 (RCM 2009-1099). The document was entered into DARRTS on 6-7-2010 by Yasmin Choudhry.

1. The duration of Communication Plan should be stated. The Communication Plan states the DHCP letter will be distributed within 60 days of the REMS approval and that information will be posted on the website within 10 days of approval but does not state when the Communication Plan will end. There should be a statement specifying the end date of the Communication Plan.
2. The approval letter for the REMS should include the following information required for the assessment of the Communication Plan:
 - a. The date of launch of the communication plan
 - b. The number of recipients in the DCHP letter distribution
 - c. Date(s) of distribution of the DHCP letter
 - d. A copy of all documents included in each distribution

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/

MICHELLE A MARSH
06/08/2010

SUZANNE BARONE
06/08/2010



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

FACSIMILE TRANSMITTAL SHEET

DATE: June 4, 2010

To: Mike Belman	Eunice Chung
Company: Schering-Plough	From: Division of Pulmonary and Allergy Drug Products
Fax number: Secure email	Fax number: 301-796-9728
Phone number: N/A	Phone number: 301-796-2300

Subject: NDA 22518 Information Request DUE June 8, 2010

Total no. of pages including cover:

Comments:

Document to be mailed: YES xNO

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Your NDA submission, NDA 22-518, dated March 5, 2010, is currently under review. We have the following request for information.

A. REMS Goals:

Revise the goals of the REMS as follows:

The goals of this REMS are:

1. To inform healthcare providers and prescribers about:
 - a. the increased risk of asthma-related death and other serious outcomes associated with the long acting beta₂-adrenergic agonists (LABA), including Dulera.
 - b. the appropriate use of the long acting beta₂-adrenergic agonists (LABA), including Dulera.
2. To inform patients:
 - a. that people with asthma who take long-acting beta₂-adrenergic agonist (LABA) medicines, such as formoterol fumarate (one of the medicines in Dulera), have been associated with a higher risk of death from asthma problems.
 - b. about the other serious risks associated with the use of Dulera.

B. Medication Guide:

Comments on the Medication Guide will be sent separately. Your Medication Guide distribution plan is acceptable.

C. Communication Plan:

1. Submit the REMS communication materials to be distributed by the professional societies. Clarify if these are different from the printed and web-based material.
 - a. Describe and submit in the REMS and the REMS Supporting Document the actual materials being communicated from professional societies to the targeted prescribers.
2. You propose to make available the educational programs and materials through the Merck web site within 10 days of the REMS approval.
 - a. Specify the length of time this material will be posted on the website.
 - b. Specify what control you have over the content of the Dulera Communication Plan on the Merck website.

- c. Submit the actual web-based educational material intended on the website
3. You propose to distribute the DHCPL to the HCPs within 60 days of the modified REMS approval. This is acceptable. Specify:
 - a. How you plan to distribute the DHCPL e.g., via direct mail etc.
 - b. How often the DHCPL will be distributed; submit a timeline for the DHCPL distribution.
 - c. See our preliminary edits for the DHCPL in Appendix A.
4. Your proposed targeted audience for the Dulera Communication Plan includes allergists, immunologists and pulmonologists, and select primary care physicians.
 - a. Specify which primary care physicians you plan to include in the list.
5. Submit a timeline for distributing REMS communication material from the professional societies to the targeted prescribers.
6. Add the following professional societies to your communication plan:
 - a. American College of Chest Physicians (ACCP)
 - b. American College of Physicians (ACP)
 - c. National Medical Association (NMA)
 - d. American Academy of Nurse Practitioners (AANP)
 - e. American Academy of Physician Assistants (AAPA).

D. Timetable for Submission of Assessments:

Your proposal to submit the Dulera REMS assessments to FDA (b) (4) from the date of approval is not acceptable. As per the February 18, 2010, REMS Notification Letter, you are required to submit the REMS assessments annually. You will be notified if the Agency at some point determines if the REMS assessments on an annual basis is no longer needed.

E. REMS Assessments Plan:

1. Your REMS Assessment Plan should also include the following information:
 - a. The date of launch of the communication plan
 - b. The number of recipients in the DCHP letter distribution
 - c. Date(s) of distribution of the DHCP letter
 - d. A copy of all documents included in each distribution
2. Regarding the physicians' and patients' surveys:

The submitted methodology lacks sufficient detail to complete a review. Submit for review the detailed plan that will be used to evaluate patients' understanding about the risks associated with and safe use of Dulera. This information does not need to be submitted for FDA review prior to approval of your REMS, however it should be submitted at least 90 days before the evaluation will be conducted. The submission should be coded "REMS Correspondence." The submission should include all methodology and instruments that will be used to evaluate the patients' knowledge about the risks associated with and safe use of Dulera.

- a. Your proposal includes an assessment of healthcare providers' comprehension of communication and education regarding Dulera. While we encourage you to study healthcare provider comprehension, this is not a necessary component of your Medication Guide –only REMS assessment.
- b. Your proposal includes an assessment of patients' comprehension of educational activities, including the Medication Guide. While we encourage you to study patients' comprehension of the Medication Guide, this is not a necessary component of your REMS assessment. The assessment is to evaluate the effectiveness of the REMS in achieving the goal by evaluating patients' knowledge of the serious risks associated with use of Dulera. The assessment is not to evaluate consumer comprehension of the Medication Guide. Respondents should not be offered an opportunity to read or see the Medication Guide again prior to taking the survey.
- c. Recruit respondents using a multi-modal approach. For example, patients could be recruited online, through physicians' offices, through pharmacies, managed care providers, or through consumer panels.
 - i) Explain how often non-respondent follow-up or reminders will be completed, and the planned frequency.
 - ii) Explain how an incentive or honorarium will be offered, and the intended amount.
 - iii) Explain how recruitment sites will be selected.
 - iv) Submit for review any recruitment advertisements.
- d. Define the sample size and confidence associated with that sample size.
- e. Define the expected number of patients to be surveyed, and how the sample will be determined (selection criteria)
- f. Explain the inclusion criteria; that is, who is an eligible respondent. For example, patient respondents might be:
 - Age 18 or older
 - Currently taking Dulera or have taken in past 3 months
 - Not currently participating in a clinical trial involving Dulera
 - Not a healthcare provider

Submit any screener instruments, and if any quotas will be used.

- g. Explain how surveys will be administered, and the intended frequency.

Offer respondents multiple options for completing the survey. This is especially important for inclusion of the lower literacy population. For example, surveys could be completed online or through email, in writing or by mail, over the phone, or in person. Explain how surveyors will be trained.

- h. Explain controls used to compensate for the limitations or bias associated with the methodology
- i. The patient sample should be demographically representative of the patients who use Dulera. If possible and appropriate, sample should be diverse in terms of: age, race, ethnicity, sex, socio-economic status, education level, geography
- j. Submit for review the introductory text that will be used to inform respondents about the purpose of the survey. Potential respondents should be told that their answers will not affect their ability to receive or take Dulera, and that their answers and personal information will be kept confidential and anonymous.
- k. Respondents should not be eligible for more than one wave of the survey.
- l. Submit for review the survey instruments (questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in the Medication Guide.
- m. The patient knowledge survey should include a section with questions asking about the specific risks or safety information conveyed in the Medication Guide to see if the patient not only understands the information, but knows what to do if they experience the event. Most of the risk-specific questions should be derived from information located in the "What is the Most Important Information I should know about Dulera?" section of the Medication Guide. The questions should be about understanding the risk, the symptoms, and what to do if the event occurs. The risk-specific questions should be non-biased, non-leading, multiple choice questions with the instruction to "select all that apply." Each question should have an "I don't know" answer option. The order of the multiple choice responses should be randomized on each survey.
- n. The order of the questions should be such that the risk-specific questions are asked first, followed by questions about receipt of the Medication Guide. Demographic questions should be collected last or as part of any screener questions. Respondents should not have the opportunity or ability to go back to previous questions in the survey. Explain if and when any education will be offered for incorrect responses.
- o. Include questions about receipt of the Medication Guide in the patient survey as a way to fulfill the obligation to report on the distribution of the Medication Guide.
- p. Just prior to the questions about receipt of the Medication Guide, include text that describes a Medication Guide. For example, Now we are going to ask you some questions about the Medication Guide you may have received with

Dulera. The Medication Guide is a paper handout that contains important information about the risks associated with use of Dulera and how to use Dulera safely. Medication Guides always include the title “Medication Guide”.

- q. Use the following (or similar) questions to assess receipt and use of the Medication Guide.
- Who gave you the Medication Guide for Dulera? (Select all that apply)
 - a) My doctor or someone in my doctor’s office
 - b) My pharmacist or someone at the pharmacy
 - c) Someone else - please explain: _____
 - d) I did not get a Medication Guide for Dulera
 - Did you read the Medication Guide?
 - a) All,
 - b) Most,
 - c) Some,
 - d) None
 - Did you understand what you read in the Medication Guide?
 - a) All,
 - b) Most,
 - c) Some,
 - d) None
 - Did someone offer to explain to you the information in the Medication Guide?
 - a) Yes, my doctor or someone in my doctor’s office
 - b) Yes, my pharmacist or someone at the pharmacy
 - c) Yes, someone else – please explain: _____
 - d) No
 - Did you accept the offer? Yes or No
 - Did you understand the explanation that was given to you?
 - a) All,
 - b) Most,
 - c) Some,
 - d) None
 - Did or do you have any questions about the Medication Guide? Yes or No (If Yes, list your question(s) below) Note: This is an open text field that should be grouped/coded by the sponsor prior to submitting to FDA
- r. Results should be analyzed on an item-by-item or variable-by-variable basis. The data may be presented using descriptive statistics, such as sample size, mean, standard deviation, median, minimum and maximum (for continuous variables), and frequency distributions (for categorical variables).
- s. Data may be stratified by any relevant demographic variable, and also presented in aggregate. We encourage you to submit with your assessments

all methodology and instruments that were used to evaluate the effectiveness of the REMS.

F. General comments:

1. Submit your proposed REMS and other materials in WORD format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS and appended materials be a single WORD document. All REMS materials should be free of promotional language and tone.
2. Consider these comments interim comments. You will receive additional comments on your proposed REMS, REMS materials, and REMS supporting document as we continue our review of the application.

2 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Please submit a response via email by COB June 08, 2010, to Eunice.Chung@fda.hhs.gov. The official response should be submitted to the NDA shortly after as well. If you have any questions, please contact Eunice Chung, Regulatory Project Manager, at 301-796-4006.

Drafted by: EChung/4JUN2010

Initialed by: SLimb/4JUN2010
SSeymour/4JUN2010
SBarnes/4JUN2010

Finalized by: EChung/4JUN2010

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

06/04/2010



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

FACSIMILE TRANSMITTAL SHEET

DATE: June 4, 2010

To: Mike Belman	Eunice Chung
Company: Schering-Plough	From: Division of Pulmonary and Allergy Drug Products
Fax number: Secure email	Fax number: 301-796-9728
Phone number: N/A	Phone number: 301-796-2300

Subject: **NDA 22518 Information Request DUE June 8, 2010**

Total no. of pages including
cover:

Comments:

Document to be mailed: YES xNO

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Your NDA submission, NDA 22-518, dated May 21, 2009, is currently under review. We have the following request for information.

1. Provide values for the table below for P04073 and P04334. Provide a similar table for P04431 with the relevant treatment arms (MF/F 100/5, MF/F 200/5, and MF 200).

Clinically judged deterioration in asthma or reduction in lung function	MF/F N (%)	MF	F	Placebo
Decrease in FEV1†				
Decrease in PEF‡				
Emergency treatment				
Hospitalization				
Treatment with additional asthma medication				

† Decrease in absolute FEV1 below the treatment period stability limit (defined as 80% of the average of the two predose FEV1 measurements taken 30 minutes and immediately prior to the first dose of randomized trial medication)

‡ Decrease in AM or PM peak flow rate below the treatment period stability limit (defined as 80% of the AM or PM PEFR obtained over the last 7 days of the run-in period)

Please submit a response via email by COB June 08, 2010, to Eunice.Chung@fda.hhs.gov. The official response should be submitted to the NDA shortly after as well. If you have any questions, please contact Eunice Chung, Regulatory Project Manager, at 301-796-4006.

Drafted by: SLimb/4JUN2010

Initialed by: SSeymour/4JUN2010
SBarnes/4JUN2010

Finalized by: EChung/4JUN2010

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EUNICE H CHUNG

06/04/2010



NDA 22-518

NDA ACKNOWLEDGMENT

Schering-Plough
2000 Galloping Hill Road
Kenilworth, NJ 07033-0530

Attention: Susan Yule
Senior Manager and Liaison, Global Regulatory Affairs

Dear Ms. Yule:

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

Name of Drug Product: Dulera (mometasone furoate/formoterol fumarate) Inhalation Aerosol
(b) (4) 100/5 and 200/5 µg

Date of Application: May 21, 2009

Date of Receipt: May 22, 2009

Our Reference Number: NDA 22-518

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 July 21, 2009, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

Please note that you are responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) (42 USC §§ 282(i) and (j)), which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) (42 USC § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices. FDAAA requires that,

at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) control numbers. 42 USC 282(j)(5)(B). You did not include such certification when you submitted this application. You may use Form FDA 3674, *Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank*, to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trials referenced in this application. Additional information regarding the certification form is available at: http://internet-dev.fda.gov/cder/regulatory/FDAAA_certification.htm. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information on registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

The NDA number provided above should be cited 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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, call me, at (301) 796-4006.

Sincerely,

{See appended electronic signature page}

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

Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Eunice Chung

6/3/2009 02:05:46 PM

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

*****Pre-decisional Agency Information*****

Memorandum

Date: June 3, 2010

To: Eunice Chung, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
(DPARP)

From: Roberta Szydlo, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications
(DDMAC)

Through: Katie Klemm, Regulatory Review Officer
(DDMAC)

CC: Lisa Hubbard, Professional Group Leader
Sangeeta Vaswani, DTC Group Leader
Robyn Tyler, Regulatory Review Officer
Wayne Amchin, Regulatory Health Project Manager
(DDMAC)

Subject: NDA # 022518
DDMAC labeling comments for DULERA[®] 100 mcg/5 mcg
(mometasone furoate 100 mcg and formoterol fumarate dihydrate 5
mcg) and 200 mcg/5 mcg (mometasone furoate 200 mcg and
formoterol fumarate dihydrate 5 mcg) Inhalation Aerosol

DDMAC has reviewed the revised proposed product labeling (PI) for DULERA[®] submitted for consult on April 30, 2010. DDMAC's comments are based on the proposed draft marked-up labeling titled "10_05_03 22518 dulera PI marked.doc" that was sent via email from DPARP to DDMAC on May 25, 2010.

Please note that comments concerning the PPI and Medication Guide will be provided under separate cover at a later date.

DDMAC's comments on the PI are provided directly in the marked-up document attached (see below).

Thank you for the opportunity to comment on these proposed materials.

If you have any questions regarding the PI, please contact Roberta Szydlo at (301) 796-5389 or roberta.szydlo@fda.hhs.gov.

27 pages of Draft Labeling 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
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FUMARATE

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/s/

ROBERTA T SZYDLO

06/03/2010



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

FACSIMILE TRANSMITTAL SHEET

DATE: June 2, 2010

To: Mike Belman	Eunice Chung, RPM
Company: Schering-Plough	From: Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: Secure E-mail	Fax number: 301-796-9728
Phone number: N/A	Phone number: 301-796-4006

Subject: Nonclinical Information Request

Total no. of pages including cover: 2

Comments: Please provide a response by June 7, 2010

Document to be mailed: YES xNO

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Your submission dated March 5, 2010, to NDA 22-518, is currently under review. We have the following request for clarification:

1. Explain the basis of your calculations for the portions underlined below:

8.1 Pregnancy

Mometasone Furoate: Teratogenic Effects

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 for adults on an area under the curve (AUC) basis. Similar effects were not observed at approximately 4 times MRHD for adults on an AUC basis.

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 in adults 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 in adults on an AUC basis).

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

adults) 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 for adults). 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)} human exposure at the MRHD for adults). Increases in leiomyomas of the rodent female genital tract have been similarly demonstrated with other beta-agonist drugs.

Reproductive Toxicology Studies

Mometasone furoate:

When rats received subcutaneous doses of mometasone furoate throughout pregnancy or during the later stages of pregnancy, 15 mcg/kg (approximately 8 times (see Section 8.1) the MRHD for adults 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 (See Section 8.1) the MRHD for adults on an AUC basis).

Please provide a response via email to Eunice.Chung@fda.hhs.gov by June 7, 2010. Your response must also be submitted to the NDA as well. If you have any questions, please contact Eunice Chung, Regulatory Project Manager, at 301-796-4006.

NDA #22-518

Drafted by: EChung/2JUN2010
Initialed by: TRobison/2JUN2010
 MShea/2JUN2010
 SBarnes/2JUN2010

Finalized by: EChung/2JUN2010

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

06/02/2010



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

Memorandum of Facsimile Correspondence

Date: May 17, 2010

To: Michael Belman
Director, Global Regulatory Affairs

Company: Schering-Plough

Fax: 908-740-2243

Phone: 908-740-4997

From: Miranda Raggio
Senior Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: NDA 22518 Re: CMC Information Request

of Pages including cover: 3

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Thank you.

Your submission to NDA 22518 dated March 5, 2010, is currently under review. We have the following request for information related to the mometasone furoate monotherapy products (single drug comparators) used in your clinical studies C97-208, C97-225, and I97-200:

Provide a summary of any and all changes to the mometasone furoate comparators used in these clinical studies, compared to the comparators described in your original NDA [Section 3.2.P.2.2, subsection 1.2 Clinical Trial Formulae, Table 23, etc.]. The batch numbers are listed below for the above-mentioned clinical studies. Alternatively, the comparison may be to your proposed to-be-marketed drug product. Such differences would include, but are not limited to, qualitative and quantitative composition, manufacturing site, manufacturing process, valve, mouthpiece, canister, stability, performance (e.g., delivered dose uniformity, delivered dose uniformity through life and aerodynamic particle size distribution). Provide summary performance data (at release and stability) and compare the data with that from the comparators described in your NDA or with the proposed to-be-marketed drug product.

Following are the relevant clinical study numbers, product strengths and batch numbers:

C97-208

MF 25 (No. 38101-037)

MF 100 (No. 38101-039)

MF 200 (No. 38101-040)

C97-225

MF 25 (No. 38101-037)

MF 100 (No. 38101-042)

I97-200

MF 50 (No. 38101-038)

MF 100 (No. 38101-042)

MF 200 (No. 38101-043)

Submit your response to the nonclinical request for information to me via email at Miranda.Raggio@fda.hhs.gov by COB on May 21, 2010. Your response will subsequently need to be officially submitted to the IND.

If you have questions, please contact Miranda Raggio at 301-796-2109.

NDA 22518

Drafted by M. Raggio/5-17-10

Initialed by Sandy Barnes/5-17-10

Alan Schroeder/5-17-10

Prasad Peri/5-17-10

Finalized by M. Raggio/5-17-10

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/

MIRANDA B RAGGIO

05/17/2010



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

FACSIMILE TRANSMITTAL SHEET

DATE: May 7, 2010

To: Mike Belman	From: Eunice Chung
Company: Schering-Plough	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: Secure email	Fax number: 301-796-9728
Phone number: N/A	Phone number: 301-796-4006
Subject: NDA 22518 Fax #10	

Total no. of pages including cover:

Comments:

Document to be mailed: YES xNO

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Your NDA submission, dated February 12, 2010, to NDA 22-518, is currently under review. The following comments are in reference to the proposed pediatric plan:

- 1) In the context of ongoing discussions regarding the long-term safety of long-acting beta-agonists (LABA) in asthma, the use of a low dose of inhaled corticosteroid (ICS) in an ICS/LABA combination is a concern. Based on information provided in the adult program, mometasone furoate and formoterol fumarate (MF/F) doses higher than (b) (4) may be appropriate in the pediatric population. We recommend that you evaluate higher dose levels in patients 5 to 11 years of age and justify the dose range proposed for evaluation in the pediatric population.
- 2) You will be required to provide the appropriate CMC data to support the new, low-dose formulation, (b) (4). This would include *in vitro* data to assess potential pharmaceutical interactions between mometasone furoate (b) (4) and formoterol fumarate (b) (4).

If you should have any questions and/or comments, please submit them by May 20, 2010 to the NDA.

Drafted by: SLimb/May 3, 2010
Initialed by:SSeymour/May 3, 2010
SBarnes/7May2010
Finalized by:EChung/7May2010

Drafted by: EChung/4MAY2010
Initialied by: SLimb/3MAY2010
 SSeymour/3MAY2010
 SBarnes/7MAY2010
Finalized by: Echung/7MAY2010

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22518

ORIG-1

SCHERING CORP

MOMETASONE
FUROATE/FORMOTEROL
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/s/

EUNICE H CHUNG

05/07/2010



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

Memorandum of Facsimile Correspondence

Date: May 26, 2010

To: Michael Belman
Director, Global Regulatory Affairs

Company: Schering-Plough

Fax: 908-740-2243

Phone: 908-740-4997

From: Miranda Raggio
Senior Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: NDA 22518 Re: PMR

of Pages including cover: 3

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Thank you.

Your submission dated May 22, 2009, to NDA 22518 for Dulera is currently under review. We have the following post-marketing requirement comment:

As discussed in the teleconference on May 20, 2010, FDA has determined that if DULERA HFA (mometasone and formoterol) is approved, you will be required to conduct one or more postmarketing clinical trials with DULERA HFA (mometasone and formoterol) compared to inhaled corticosteroids in adults and adolescent patients with asthma to evaluate the risk of serious asthma outcomes (asthma related death, intubations, and hospitalizations). Submit your agreement to conduct the required clinical trial(s). As the design of the clinical trial(s) for long-acting beta agonists products is under active discussion, we recommend you submit a proposal for study design for consideration.

Submit your response to Eunice Chung at Eunice.Chung@fda.hhs.gov by COB Wednesday, June 2, 2010. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact Miranda Raggio, Senior Regulatory Project Manager, at 301-796-2109 on May 26, 2010, or Eunice Chung after May 26th.

NDA 22518

Drafted by M. Raggio/5-26-10

Initialed by Sandy Barnes/5/26/10

Susan Limb/5/26/10

Sally Seymour/5-26/10

Finalized by M. Raggio/5/26/10

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22518

ORIG-1

SCHERING CORP

MOMETASONE
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FUMARATE

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/s/

MIRANDA B RAGGIO

05/26/2010



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

Memorandum of Facsimile Correspondence

Date: May 25, 2010

To: Michael Belman
Director, Global Regulatory Affairs

Company: Schering-Plough

Fax: 908-740-2243

Phone: 908-740-4997

From: Miranda Raggio
Senior Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: NDA 22518 Re: Labeling Information Request

of Pages including cover:

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Thank you.

Your supplemental NDA submission dated May 22, 2009, for Dulera (mometasone furoate/formoterol fumarate) is currently under review. We have the following comments pertaining to the draft labeling submitted on March 6, 2010. Additional comments may be forthcoming.

1. Figures 1 and 2: Identify the treatment groups depicted in the respective curves. Provide the statistical test used to derive the p value with each figure.
2. The numerical values presented in Sections 8 and 13 are based on the Agency's review. Provide justification if different values are proposed.
3. Submit revised labeling as shown in the marked-up attached label.

Submit your response via email to Eunice Chung at Eunice.Chung@fda.hhs.gov by COB on Monday, June 7, 2010. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact Miranda Raggio at 301-796-2109 prior to and on May 26, and Eunice Chung at 301-796-4006 after May 26, 2010. Thank you.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22518

ORIG-1

SCHERING CORP

MOMETASONE
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/s/

MIRANDA B RAGGIO

05/25/2010



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

Memorandum of Facsimile Correspondence

Date: May 18, 2010

To: Michael Belman
Director, Global Regulatory Affairs

Company: Schering-Plough

Fax: 908-740-2243

Phone: 908-740-4997

From: Miranda Raggio
Senior Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: NDA 22518 Re: Clinical Pharmacology Labeling Information Request

of Pages including cover: 3

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Thank you.

Your submission to NDA 22518 dated March 5, 2010, is currently under review. We have the following request for information:

1. Clarify the specific dose of Dulera given to achieve the Tmax value ranging from 0.167 to (b) (4) hour in the following paragraph:

Section 12.3 Pharmacokinetics *Formoterol fumarate*:

*Healthy Subjects: When DULERA was administered to healthy subjects, formoterol was absorbed with median Tmax values ranging from 0.167 to (b) (4) hour. In a single-dose study with DULERA 400 mcg/10 mcg in healthy subjects, arithmetic mean (CV%) Cmax and AUC for formoterol were 15 (50) pmol/L and 81 (51) pmol*h/L, respectively. Over the dose range of 10 to 40 mcg for formoterol from DULERA, the exposure to formoterol was dose proportional.*

2. Clarify the specific dose of Dulera given to achieve the Tmax value ranging from 0.58 to 1.97 hours in the following paragraph:

Section 12.3 Pharmacokinetics *Formoterol fumarate*:

*Asthma Patients: When DULERA was administered to patients with asthma, formoterol was absorbed with median Tmax values ranging from 0.58 to 1.97 hours. (In a single-dose study with DULERA 400 mcg/10 mcg in patients with asthma, arithmetic mean (CV%) Cmax and AUC0-12h for formoterol were 22 (29) pmol/L and 125 (42) pmol*h/L, respectively. Following multiple-dose administration of DULERA 400 mcg/10 mcg, the steady-state arithmetic mean (CV%) Cmax and AUC0-12h for formoterol were 41 (59) pmol/L and 226 (54) pmol*hr/L.*

3. Provide appropriate data source to show how the Tmax values were obtained.

Submit your response to this request for information to me via email at Miranda.Raggio@fda.hhs.gov by COB on May 21, 2010. Your response will subsequently need to be officially submitted to the IND.

If you have questions, please contact Miranda Raggio at 301-796-2109.

NDA 22518

Drafted by M. Raggio/5-14-10
Initialed by Sandy Barnes/5-18-10
Ying Fan/5-18-10
Yun Xu/5-18-10
Finalized by M. Raggio/5-18-10

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/

MIRANDA B RAGGIO

05/18/2010

MEMORANDUM

NDA: 22-518
Sponsor: Schering-Plough and Novartis
Drug: Dulera (Mometasone furoate / Formoterol fumarate)
Inhalation Aerosol
Submission Date: February 16, 2010
Indication: Asthma [REDACTED] ^{(b) (4)} in adults
and children 12 years of age and older
Reviewer: Ying Fan, Ph.D.
Team Leader (Acting): Yun Xu, Ph.D
Memo Date: May 12, 2010

Introduction

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 (MF) inhalation powder (ASMANEX® TWISTHALER® 110 and 220 mcg) is approved in the US for maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older. Formoterol fumarate (F) inhalation powder (FORADIL® AEROLIZER® 12 mcg) is approved in the US for twice-daily (morning and evening) administration in the maintenance treatment of asthma and in the prevention of bronchospasm in adults and children 5 years of age and older with reversible obstructive airways disease, including patients with symptoms of nocturnal asthma.

Administrative and Regulatory History

The original NDA 22-518, a 505(b) (1) application was submitted on May 21, 2009 and the original clinical pharmacology review due date was January 22, 2010. On January 22, 2010 the original clinical pharmacology review was placed in Darrrts. The Sponsor submitted a new efficacy study report on February 16, 2010 and new proposed labeling on March 5, 2010. Therefore, the PUDUFA date has been extended to June 22, 2010.

Clinical Pharmacology Finding:

There are no additional Clinical Pharmacology studies to be reviewed from the Clinical Pharmacology perspective in the submissions on February 16, 2010 and on March 5, 2010.

Labeling Recommendations:

The sponsor changed most of the labeling based on our recommendation on February 5, 2010. However, we need some clarification on some minor issues below.



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/

YING FAN
05/13/2010

YUN XU
05/14/2010

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:
CDER-DDMAC-RPM

FROM: (Name/Title, Office/Division/Phone number of requestor)
Eunice Chung, RPM, DPARP, 301-796-4006

REQUEST DATE
April 30, 2010

IND NO.

NDA/BLA NO.
NDA 22-518

TYPE OF DOCUMENTS
(PLEASE CHECK OFF BELOW)

NAME OF DRUG
Dulera (mometasone/formoterol)

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG
Long Acting Beta Agonist-Respiratory

DESIRED COMPLETION DATE
(Generally 1 week before the wrap-up meeting)
May 28th, if possible. If not, June 5th

NAME OF FIRM:

Schering/Merck

PDUFA Date: June 22, 2010

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:

(Check all that apply)

- PACKAGE INSERT (PI)
- PATIENT PACKAGE INSERT (PPI)
- CARTON/CONTAINER LABELING
- MEDICATION GUIDE
- INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION

- ORIGINAL NDA/BLA
- IND
- EFFICACY SUPPLEMENT
- SAFETY SUPPLEMENT
- LABELING SUPPLEMENT
- PLR CONVERSION

REASON FOR LABELING CONSULT

- INITIAL PROPOSED LABELING
- LABELING REVISION

EDR link to submission:

<\\CDSESUB1\EVSPROD\NDA022518\022518.enx>

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: N/A

Labeling Meetings: May 28, 2010, Tecon-June 2, 2010

Wrap-Up Meeting: May 12, 2010

The receipt date of the revised labeling is March 8, 2010 and is available in DARRTs. It was coded as "REMS AMENDMENT." The PI may change with regard to the efficacy data. We will have the SCPI to you by May 24, 2010. Please let me know if you have any questions. Thank you.

SIGNATURE OF REQUESTER

Eunice H. Chung

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)

- eMAIL
- HAND

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22518

ORIG-1

SCHERING CORP

MOMETASONE
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/s/

EUNICE H CHUNG

04/30/2010



NDA 22-518

REQUEST FOR METHODS VALIDATION MATERIALS

Schering-Plough
Attention: Greg Howe
Senior Manager and Liaison
Global Regulatory Affairs-CMC
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Dr. Howe:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dulera (mometasone furoate and formoterol fumarate) Inhalation Aerosol, (b) (4)
mometasone furoate 100 mcg and formoterol fumarate dihydrate 5 mcg inhalation aerosol.

We will be performing methods validation studies on Dulera (mometasone furoate and formoterol fumarate) Inhalation Aerosol, (b) (4)
mometasone furoate 100 mcg and formoterol fumarate dihydrate 5 mcg inhalation aerosol, as described in NDA 22-518.

In order to perform the necessary testing, we request the following sample materials and equipments:

(b) (4)

A large rectangular area of the document is completely redacted with a solid grey fill, obscuring all text and graphics that would have been present in this section.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: James F. Allgire
1114 Market Street, Room 1002
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

James F. Allgire
Team Leader
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/

JAMES F ALLGIRE

04/19/2010

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

CONSULTATIVE REQUEST FOR METHODS VALIDATION

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

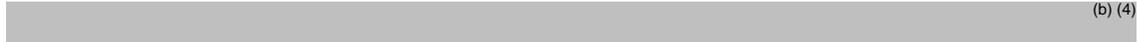
FROM: Alan C. Schroeder, Ph.D., Acting CMC Lead, Branch II, DPAI, ONDQA
E-mail Address: alan.schroeder@fda.hhs.gov
Phone: (301)-796-1749
Fax.: (301)-796-9747

Through: Dr. Prasad Peri, Acting Branch Chief, Branch II, DPAI, ONDQA
Phone: (301)-796-1730

SUBJECT: Methods Validation Request

Application Number: **NDA 22-518**

Name of Product: Dulera (mometasone furoate and formoterol fumarate) Inhalation Aerosol

 (b) (4)
mometasone furoate 100 mcg and formoterol fumarate dihydrate 5 mcg inhalation aerosol
mometasone furoate 200 mcg and formoterol fumarate dihydrate 5 mcg inhalation aerosol

Applicant: Schering-Plough (now merged with Merck)

Applicant's Contact Person: Greg Howe, Senior Manager and Liaison, Global Regulatory Affairs - CMC

Address: 2000 Galloping Hill Road, Kenilworth, NJ 07033

Telephone: 908-740-2948 Fax: 908-740-5100

The link to the electronic Methods Validation Package is the following:

\\cdsesub1\EVSPROD\NDA022518\0019\m3\32-body-data\32r-reg-info\methods-validation-package.pdf
(NDA 22-518_Amendment dated 2/03/2010)

Date NDA Received by CDER: 5/22/2009

Chemical/Therapeutic Type: 4S

Date of Amendment(s) containing the MVP: **2/03/2010**

Special Handling Required: No

DATE of Request: **4/09/2010**

DEA Class: N/A

Requested Completion Date: **9/09/2010**

PDUFA User Fee Goal Date: **06/22/2010**

This is to confirm the suitability of the proposed manufacturing controls as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request Form*. Upon receipt of the samples, please notify the review chemist via email to the email address cited above. Perform the tests indicated in item 3 of the attached *Methods Validation Request Form* as described in the accompanying MV package. In addition to including a summary of laboratory results, please also include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes. All information relative to this application is to be held confidential as required by 21 CFR 314.430.

Because of statutory time limits for processing applications, we request your report to be submitted promptly upon completion, but not later than 45 days from date of receipt of the required samples, laboratory safety information,

equipment, components, etc. Please promptly advise the reviewing chemist of the date the validation process begins. If the requested completion date cannot be met, please promptly notify the reviewing chemist.

Upon completion of the requested validation/verification, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying memoranda). At the bottom of the report signed by the laboratory director or by someone designated by the director, place the filing code: "**MR/Method Validation Report.**" Send by overnight courier to the above reviewing chemist.

ENCLOSURE: *Methods Validation Request Form.*

MVP Reference #	METHODS VALIDATION REQUEST FORM		NDA # 22-518
← SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT			
ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION	
See MV package (2/03/2010 amendment) available through Electronic Document Room and GlobalSubmit Review, Section 1, pp. 3-5.			
↑ Contents of Attached Methods Validation Package:		Volume/Page Number(s)	
Statement of Composition of Finished Dosage Form(s)		Section 2 of the 2/03/2010 amendment (GlobalSubmit Review), pp. 8-10	
Specifications/Methods for New Drug Substance(s)		Not provided (verification not requested for drug substance methods)	
Specifications/Methods for Finished Dosage Form(s)		Section 2 of the 2/03/2010 amendment (GlobalSubmit Review), pp. 11-178	
Supporting Data for Accuracy, Specificity, etc.		Section 3 of the 2/03/2010 amendment (GlobalSubmit Review), pp. 179-421	
Applicant's Test Results on NDS and Dosage Forms		Section 3 of the 2/03/2010 amendment (GlobalSubmit Review), NDS not included, pp. 422-503; Section 4, pp. 504-604	
Other: MSDS information for drug substances and drug product		Section 5 of the 2/03/2010 amendment (GlobalSubmit Review), pp. 605-672	
→ REQUESTED DETERMINATIONS (Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.)			
Method ID	Method Title	Volume/Page	MV Request Category (see attached page)
DRUG PRODUCT			
(b) (4)			

Additional Comments:

Methods Validation Request Criteria

MVP Request Category	Description
1	Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)
2	Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms)
3	Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)
4	Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)
5	Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method)
6	Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluding peaks, limits of detection and/or quantitation)
7	Methods that are subject to a “for cause” reason.

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/

ALAN C SCHROEDER
04/09/2010

PRASAD PERI
04/09/2010
I concur

MICHAEL M FOLKENDT
04/14/2010

Chung, Eunice

From: Greeley, George
Sent: Thursday, March 04, 2010 10:17 AM
To: Chung, Eunice
Cc: Stowe, Ginneh D.
Subject: NDA 22-518 Dulera

Importance: High

Follow Up Flag: Follow up
Flag Status: Red

Hi Eunice,

The Dulera (mometasone furoate/formoterol fumarate) partial waiver, deferral, plan and assessment was reviewed by the PeRC PREA Subcommittee on March 03, 2010.

The Division recommended a partial waiver for pediatric patients 0-4 years because product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulations AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulations. The Division recommended a deferral for patients 5-11 years of age (b) (4)

(b) (4)

The PeRC agreed with the Division to grant a partial waiver for patients 0-4 years and deferral for patients 5-11 years and that the PREA PMR has been fulfilled for patients 12-17 years of age.

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
FDA/CDER/OND
10903 New Hampshire Avenue
Bldg. 22, Room 6467
Silver Spring, MD 20993-0002
Phone: 301.796.4025
Email: george.greeley@fda.hhs.gov

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

FACSIMILE TRANSMITTAL SHEET

DATE: February 26, 2010

To: Mike Belman	From: Eunice Chung
Company: Schering-Plough	Division of Pulmonary and Allergy Drug Products
Fax number: Secure email	Fax number: 301-796-9728
Phone number: N/A	Phone number: 301-796-2300

Subject: NDA 22518 Comments

Total no. of pages including cover:

Comments:

Document to be mailed: YES xNO

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

Drafted by: EChung/25FEB2010
Initialied by: BAbugov/25FEB2010
JBuenconsejo/25FEB2010
SBarnes/26FEB2010
Finalized by: Echung/26FEB2010

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22518

ORIG-1

SCHERING CORP

MOMETASONE
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FUMARATE

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/s/

EUNICE H CHUNG

02/26/2010

INTEROFFICE MEMO

TO: NDA 22-518
Sequence number/date/type of submission: S003/May 22, 2009/original

FROM: Jean Q Wu, M.D., Ph.D.
Acting Pharmacology/Toxicology Supervisor
Division of Pulmonary and Allergy Products

DATE: February 25, 2010

I concur with the pharmacology/toxicology primary reviewer's (Dr. Timothy Robison) recommendation that the pharmacology and toxicology of Dulera[®] (Mometasone Furoate/Formoterol Fumarate) have been adequately studied and the drug product should be approved pending a final labeling review from a nonclinical perspective.

Dulera[®] is a fixed combination of mometasone furoate, a glucocorticosteroid anti-inflammatory agent, and formoterol fumarate, a long acting beta-adrenergic (LABA) bronchodilator. It is intended for treatment of asthma in patients 12 years of age and older via the oral inhalation route of administration (MDI). The individual active drugs in Dulera[®] have been approved and are currently on the market. The nonclinical safety program for Dulera[®] is based upon the complete toxicology programs conducted for both individual active drugs. The nonclinical programs for the individual active drugs include single dose, chronic, reproductive toxicology, genotoxicity, and carcinogenicity studies. As the pharmacology and toxicology profile of each active drug, mometasone furoate or formoterol fumarate, has been individually well characterized, a bridging toxicology program was considered sufficient to support the registration.

The bridging toxicology program was designed to characterize potential toxicological interactions between mometasone and formoterol. The program consisted of general inhalation toxicity studies of Dulera[®] formulation up to 13 weeks in both rats and dogs. In the 13-week toxicity studies, target organs of toxicity in rats and dogs included the heart (increases in heart rate in dogs), lung (accumulations of alveolar macrophages in rats and bronchioloalveolar hyperplasia and bronchial inflammation in dogs), trachea (decreased globule leukocytes in rats), adrenal gland (cortical atrophy and vacuolization in dogs), thymus (involution/atrophy in rats), bone marrow (increased fat deposition in rats and dogs), liver (cytoplasmic vacuolization for dogs), mammary gland, (abnormal lobuloalveolar development for rats and epithelial vacuolization for dogs), ovaries (decreased corpora lutea for rats, hypoplasia for dogs), vagina (abnormal mucification for rats), uterus (hypoplasia for dogs), and multiple organs (lymphoid depletion in both rats and dogs). The NOAELs for mometasone/formoterol in the 13-week rats and dogs were not identified based on the histopathological findings. The toxicity findings were primarily attributable to the pharmacological effects of mometasone while tachycardia observed in dogs was attributable to formoterol. These studies did not show any unexpected toxicities of two active ingredients and did not reveal any significant evidence of additive or synergistic toxic effects with the combination of mometasone and formoterol. There was no evidence of any

interactions on toxicokinetic parameters in rats or dogs. The systemic exposure (i.e., AUC) values for mometasone and formoterol achieved in the 13-week studies with rats and dogs were comparable to or greater than the exposures obtained with the highest clinical dose of 400/10 µg (mometasone/formoterol) BID.

The reproductive toxicology, genotoxicity, and carcinogenicity of individual active drugs of Dulera[®] were well characterized in the respective NDAs (Asmanex[®] NDA 21-067 for mometasone, and Foradil[®] NDA 20-831) and should be reflected in the nonclinical sections of the labeling regarding each active drug, if applicable.

Dulera[®] drug product contains the propellant, HFA-227, and two excipients, dehydrated alcohol and oleic acid that are all found in approved inhalation drug products. The HFA 227 impurities (b) (4) and the updated information of HFA-227 (b) (4) were evaluated by Dr. Timothy Robison in two separate Chemistry Consultation Request reviews dated September 3, 2009 and November 19, 2009. The proposed specifications of impurities, extractables and leacheables in Dulera[®] product were evaluated and considered acceptable by Dr. Robison in three separate Chemistry Consultation reviews dated December 4, 2009, January 5, 2010 and January 15, 2010, respectively.

The final labeling review for the current submission is deferred to a later time when the clinical decision is clear for this application after a review of the major amendment (a full clinical study report) submitted on February 16, 2010.

Jean Q Wu, M.D., Ph.D.
Acting Pharmacology/Toxicology Supervisor

Application
Type/Number

Submission
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Product Name

NDA-22518

ORIG-1

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/s/

JEAN Q WU

02/25/2010



NDA 22-518

PDUFA GOAL DATE EXTENSION

Schering-Plough Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033-0530

Attention: Michael Belman
Director & Liaison, Global Regulatory Affairs

Dear Mr. Belman:

Please refer to your February 16, 2010 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dulera (mometasone furoate/formoterol fumarate) Inhalation Aerosol (b) (4) 100/5 and 200/5.

On February 17, 2010, we received your February 16, 2010, major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is June 22, 2010.

If you have any questions, call Eunice Chung, Regulatory Project Manager, at (301) 796-4006.

Sincerely yours,

{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

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22518

ORIG-1

SCHERING CORP

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/s/

BADRUL A CHOWDHURY

02/24/2010



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

FACSIMILE TRANSMITTAL SHEET

DATE: February 19, 2010

To: Mike Belman	Eunice Chung, RPM
Company: Schering-Plough	From: Division of Pulmonary and Allergy Drug Products
Fax number: Secure E-mail	Fax number: 301-796-9728
Phone number: N/A	Phone number: 301-796-4006

Subject: CMC Information Request

Total no. of pages including cover: 2

Comments: Please provide a response to the request ASAP

Document to be mailed: YES xNO

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NDA #22-518

Your submission dated January 29, 2010, to NDA 22-518, is currently under review. We have the following comments or request for information:

With regard to your response to our comment 5b, provide a post-approval agreement to further study the changes in particle size distribution of the emitted plume over the use life of the drug product. Develop data to explain the mechanism of these changes. Include data for the ^{(b) (4)} grouping of the Cascade Impactor as well as the other groupings. As a part of this agreement, a report of the results of this study within 6 months of the date of this information request must be provided.

If you have any questions, please contact Eunice Chung, Regulatory Project Manager, at 301-796-4006.

NDA #22-518

Drafted by: ASchroeder/19FEB2010
Initialed by: PPeri/19FEB2010
SBarnes/19FEB2010

Finalized by: EChung/19FEB2010

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22518

ORIG-1

SCHERING CORP

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/s/

EUNICE H CHUNG

02/19/2010



Food and Drug Administration
 Center for Drug Evaluation and Research
 OFFICE OF DRUG EVALUATION II

FACSIMILE TRANSMITTAL SHEET

DATE: February 18, 2010

To: Mike Belman	From: Eunice Chung
Company: Schering-Plough	Division of Pulmonary and Allergy Drug Products
Fax number: Secure email	Fax number: 301-796-9728
Phone number: N/A	Phone number: 301-796-4006
Subject: NDA 22518 Labeling Comments #1	

Total no. of pages including cover:

Comments: For our discussion on February 22, 2010

Document to be mailed: YES XNO

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Thank you.

We are currently reviewing your Package Insert for NDA for Dulera, submitted May 22, 2009 and August 12, 2009. These are not our final comments. We may have additional comments as our review proceeds. Submit revised labeling incorporating these comments by February 26, 2010.

1. The boxed warning, Sections 1, 2, 5, 6, and 17 have been revised to describe the risk of asthma-related deaths and hospitalizations associated with LABAs and to maintain consistency with the new labeling for other LABA-containing products approved for asthma.
2. Include the unit of measurement, mcg, with the presentation of numerical dosage strength throughout the PI, e.g. DULERA 100 mcg/5 mcg.

(b) (4)

4. Section 5, Adverse Reactions

- a. Section 5.1, Revise to remove data for (b) (4)
- b. Section 5.2, Remove Postmarketing Data

5. Section 8.4 and 8.5, Pediatric Use and Geriatric Use

- a. Revise to remove reference to (b) (4)
- b. Recalculate sample sizes and mean data to include the pivotal trials P04334, P04431, and P04139. Provide the number of pediatric patients 12 to 17 years who received DULERA in other trials in the development program separately.

6. Section 12.3 Pharmacokinetics, Absorption

- a. Mometasone furoate:

(b) (4)

We recommend that you delete this sentence because we can not verify the numbers. If you want to keep it, provide appropriate reference or show us how you estimated the bioavailability numbers.

- b. Formoterol fumarate:

PK information for healthy and asthma patients is separated out under section 12.3. Provide the numbers for median T_{max} values separately for healthy subjects and for patients with asthma in the spaces indicated in the label.

- ii. *“The effective t_{1/2} for mometasone furoate following inhalation with DULERA was 25 hours in healthy subjects and in patients with asthma.”*

We recommend that you move this statement to the Excretion section. In addition, because we could not verify the t_{1/2} value, provide appropriate reference or show us how you estimated t_{1/2}.

The following comments pertain to the immediate container labels (trade and sample 100 mcg/5 mcg, 200 mcg/5 mcg):

1. Remove the graphic next to the tradename.
2. Redesign the immediate container labels to use larger fonts and to be more legible. You may propose an approach based on 21 CFR 201.10(h)(2).
3. 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
4. Add the statement “per actuation” to appear beside the product strength.
5. Delete or relocate to the side panel the statement: “See Package Insert for Full Prescribing Information” as this information is not needed on the principal display panel.
6. Increase the prominence of the statement: “Shake well before using” to ensure this essential information is not overlooked.
7. 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.

The following comments pertain to the carton labels:

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 prominence to ensure this information is not overlooked.
8. Include a printed “lot” and “exp” on the label.
9. Add a statement to indicate that the Dulera canister is to be used with the Dulera actuator only.
10. Add the following warning statements:

“Avoid spraying in eyes.”

“Keep out of reach of children.”

Drafted by: Echung/4FEB2010
| Initialed by: SBarnes/5FEB2010

ASchroeder/18FEB2010
Prasad Peri/18FEB2010
Bob Abugov/8FEB2010
JBuenconsejo/8FEB2010
YFan/8FEB2010
PRoy/8FEB2010
TRobison/5FEB2010
JWu/5FEB2010
Slimb on behalf of SSeymour/18FEB2010

Finalized by: Echung/18FEB2010

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22518

ORIG-1

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/s/

EUNICE H CHUNG

02/18/2010

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

****PRE-DECISIONAL AGENCY MEMO****

Memorandum

Date: February 3, 2010

To: Eunice H. Chung, Regulatory Project Manager
Division of Pulmonary and Allergy Drug Products

From: Samuel M. Skariah, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: NDA #22-518
DDMAC labeling comments for DULERA[®] 100/5 mcg and 200/5 mcg
Inhalation Aerosol

DDMAC has reviewed the proposed product labeling (PI) and carton/container labels submitted for consult on June 8, 2009. DDMAC's comments regarding the Medication Guide will be sent at a later date under separate cover after DPAP forwards the draft document to DDMAC for review.

DDMAC offers the following comments regarding the version of the proposed PI and container labels emailed on February 3, 2010.

(b) (4)



Application
Type/Number

Submission
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Product Name

NDA-22518

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/s/

SAMUEL M SKARIAH

02/03/2010



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

FACSIMILE TRANSMITTAL SHEET

DATE: January 27, 2010

To: Mike Belman	Eunice Chung
Company: Schering-Plough	From: Division of Pulmonary and Allergy Drug Products
Fax number: Secure email	Fax number: 301-796-9728
Phone number: N/A	Phone number: 301-796-2300

Subject: NDA 22518 Information Request DUE February 10, 2010

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES xNO

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Your NDA submission, NDA 22-518, dated May 22, 2010, is currently under review. We have the following request for information:

1. Provide a pediatric plan that includes a statement of intent to complete the required trial(s). The plan should include an outline of the proposed trial(s) as well as dates for each protocol submission, trial initiation, and submission of the final study report. Also, complete the following table for each proposed trial.

<p>Drug information: <i>Examples in italics</i></p> <ul style="list-style-type: none"> • Route of administration: • Formulation: • Dosage: • Regimen:
<p>Study Design:</p>
<p>Age group and population in which study will be performed:</p> <p><i>This section should list the age group and population exactly as it is in the plan.</i></p> <p><i>Example:</i> <i>Study 1: patients aged X to Y years.</i> <i>Study 2: sufficient number of subjects to adequately characterize the pharmacokinetics in the above age groups.</i></p>
<p>Number of patients to be studied or power of study to be achieved:</p> <p><i>Example:</i></p> <p><i>Study 1: X subjects in each treatment arm and be powered to show that (drug name, concentration, form etc) DRUG is not inferior to the active comparator. 50% must be females and 25% must be less than 3 years.</i></p> <p><i>Study 2: This study is powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters.</i></p>
<p>Entry criteria:</p> <p><i>This section should list pertinent inclusion/exclusion criteria.</i></p>
<p>Clinical endpoints:</p> <p><i>Example:</i> <i>Study 1: Clinical outcome and safety will be the primary endpoints.</i> <i>Study 2: The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG should attempt to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, Cmax, Tmax, and CL/F.</i></p>
<p>Timing of assessments:</p> <p><i>Example :baseline, week 1, 4, and 6</i></p>
<p>Statistical information (statistical analyses of the data to be performed):</p> <p><i>Example:</i></p> <p><i>Study 1 non-inferiority: two-sided 95% confidence interval (CI) of treatment difference in improvement rates should be within 25% of the control's response rate.</i> <i>Study 2: descriptive statistical methods for AUC, C max, Tmax, CL/F and compared to adults.</i></p>
<p>Timeframe for submitting reports of the studies:</p> <p><i>When are studies to be completed?</i></p>
<p>Comments on Drug safety:</p>

Please submit a response via email by COB February 10, 2010, to Eunice.Chung@fda.hhs.gov. The official response should be submitted to the NDA shortly after as well. If you have any questions, please contact Eunice Chung, Regulatory Project Manager, at 301-796-4006.

Drafted by: SLimb/26JAN2010

Initialed by: SSeymour/26JAN2010
SBarnes/27JAN2010

Finalized by: EChung/27JAN2010

Application
Type/Number

Submission
Type/Number

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Product Name

NDA-22518

ORIG-1

SCHERING CORP

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EUNICE H CHUNG

01/27/2010

DATE: January 26, 2010
TO: NDA 22-518 Extended Review Team
FROM: Alan C. Schroeder, Ph.D.
THROUGH: Christine Moore, Ph.D.
SUBJECT: Considerations for Inspection (PAI) of Schering for N 22-518

NDA 22-518 was submitted by Schering Corporation for Dulera (mometasone furoate and formoterol fumarate) Inhalation Aerosol with (b) (4) drug product strengths proposed, namely, (b) (4) 100 mcg/5 mcg and 200 mcg/5 mcg mometasone furoate/formoterol fumarate dihydrate. The proposed indication is for the (b) (4) treatment of patients with asthma, in adults and children 12 years of age and older.

An overall recommendation by compliance from the pre-approval inspection has not yet been made, and the Schering site for drug product, labeling, secondary packaging and final release in Kenilworth, NJ has not yet received the indicated GMP inspection according to the EES. There are five other sites for which an acceptable OC recommendation has been made, and two other sites for which recommendations have not yet been made in EES, but which were scheduled to be inspected in October 2009.

This memo includes a discussion of a large number of corrected errors in the data submitted in the NDA. These corrected errors are raised for consideration by the Office of Compliance and the Office of Regulatory Affairs regarding pre-approval inspection.

Overview of the Dosage Form and the Drug Product Manufacturing Process:

The drug product is a pressurized metered dose inhaler which contains the active ingredients mometasone furoate anhydrous and formoterol fumarate dihydrate. These drug substances are the same as utilized in other, approved inhalation drug products. The excipients in the drug product are alcohol dehydrated (anhydrous ethanol) (b) (4) oleic acid (b) (4), and the propellant HFA-227. The micronized active ingredients form a suspension in the excipients upon shaking. The container closure system is made from a 16 mL aluminum canister with a (b) (4) (b) (4) MDI metering valve, and a (b) (4) press and breathe actuator with an integrated dose counter. The MDI is manufactured by (b) (4)

It has very recently come to our attention that an amendment was submitted with a letter date of October 29, 2009, which states that in connection with submitting the drug

application for Dulera to other countries, “some minor discrepancies/errors were noted which also affect some of the CTD sections of NDA 22-518. In response, a re-review of the NDA documentation was conducted to identify any potential data discrepancies/errors. This review has identified discrepancies in nine CTD sub-section documents which have been updated and are being re-supplied.” Information provided in the October 29, 2009 amendment appears to support the applicant’s conclusion that the identified discrepancies/errors are minor and do not affect the interpretation of the data. Nevertheless, the list of changes is approximately 9 pages in length, and just the sheer number of corrections may potentially raise the question of the data integrity in this NDA. A copy of this amendment was sent to the NJ FDA district office as per the applicant.

(b) (5)

Alan C. Schroeder, Ph.D.
Quality Reviewer/Acting Pharmaceutical Assessment Lead
301-796-1749

Prasad Peri
Acting Chief, Branch II
301-796-1730

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/

DON L HENRY
01/26/2010

ALAN C SCHROEDER
01/26/2010

PRASAD PERI
01/26/2010
I Concur



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

FACSIMILE TRANSMITTAL SHEET

DATE: January 19, 2010

To: Mike Belman	From: Eunice Chung, RPM
Company: Schering	Division of Pulmonary and Allergy Drug Products
Fax number: Secure Email	Fax number: 301-796-9728
Phone number: N/A	Phone number: 301-796-4006
Subject: Information Request (NDA 22-518)	

Total no. of pages including cover:

Comments: Please provide a response to the request by January 29, 2010

Document to be mailed: YES xNO

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Your NDA submission, NDA 22-518, is currently under review. We have the following requests for information:

1. This pertains to the drug product stability data in Tables 4 and 5 of section 3.2.P.5.6 of the original NDA, which show examples of drug product performance (DCU and APSD) (b) (4). Provide the following additional information for this 30°C/75%RH stability study.
 - a. Indicate batch number(s) and the number of canisters tested in Table 4 and Table 5.
 - b. In order to provide a better understanding of the performance of the drug product at moisture levels approaching the maximum limit (b) (4), provide similar summary data for all of the tested time points in this 30°C/75%RH stability study, and provide similar summary data for each of the proposed drug product strengths.
2. Explain the following discrepancies pertaining to the secondary reference standard COA provided in Section 3.2.P.6 for Mometasone Furoate. The COA reports (b) (4).
3. Modify your post-approval stability commitment to state that you will periodically report the results of the stability studies to the FDA. Modify the post-approval stability protocol to include the 3 and 9 month stability time points.
4. Clarify the numbering of steps in the method (b) (4) for the “end of life” determination. On page 9 (Section 3.2.P.8.3), references made to step 22, step 28 and step 9 to 19 are not clear since the higher numbered steps are not listed. Some of the text is cut off on page 14 (Section 3.2.P.8.3), under “volume added (mL)” in the “calculations” section. Rectify these issues.
5. The following comments pertain to your stability data in Section P.8.3.
 - a. Provide tabular APSD summary stability data to estimate the percentage change for drug deposited on each stage grouping (b) (4) over the proposed shelf life of the product, for each active ingredient and product strength (using analytical method (b) (4)) for drug product stored at 25°C/60%RH. Clarify how (b) (4) particle size for stage grouping (b) (4) particle size for the other stage groupings over the life of the drug product.

- b. Explain why the changes in APSD from beginning to end of can are ^{(b) (4)} [REDACTED] for the other stage groupings).

Please provide a response via email to Eunice.Chung@fda.hhs.gov by COB January 29, 2010. Your response should also be officially submitted to the NDA. If you have any questions, please contact Eunice Chung, Regulatory Project Manager, at 301-796-4006.

NDA 22-518

Drafted by: ASchroeder/15JAN2010
Initialed by: PPeri/15JAN2010
SBarnes/19JAN2010

Finalized by: Echung/19JAN2010

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

01/19/2010



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

FACSIMILE TRANSMITTAL SHEET

DATE: January 19, 2010

To: Mike Belman	From: Eunice Chung
Company: Schering-Plough	Division of Pulmonary and Allergy Drug Products
Fax number: Secure email	Fax number: 301-796-9728
Phone number: N/A	Phone number: 301-796-2300

Subject: NDA 22518 Information Request

Total no. of pages including cover:

Comments: Please respond by JANUARY 22, 2010

Document to be mailed: YES xNO

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Your NDA submission, NDA 22-518, is currently under review. We have the following request for information:

1. Provide electronic datasets for Studies C97-208 and C97-225. We are specifically interested in the efficacy variable, change in mean FEV1 from baseline. Include data on the time at which spirometry was performed.

Please submit a response via email to Eunice.Chung@fda.hhs.gov by COB January 22, 2010. The official response should be submitted to the NDA shortly after as well. If you have any questions, please contact Eunice Chung, Regulatory Project Manager, at 301-796-4006.

Drafted by: SLimb/19JAN2010
Initialied by: SSeymour/19JAN2010
SBarnes/19JAN2010

Finalized by: Echung/19JAN2010

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

01/19/2010



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

FACSIMILE TRANSMITTAL SHEET

DATE: December 23, 2009

To: Mike Belman	Eunice Chung
Company: Schering	From: Division of Pulmonary and Allergy Drug Products
Fax number: Secure Email	Fax number: 301-796-9728
Phone number: N/A	Phone number: 301-796-4006

Subject: NDA 22518 Information Request DUE JANUARY 11, 2010

Total no. of pages including cover: 2

Comments:

Document to be mailed: YES xNO

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Your NDA submission, NDA 22-518, is currently under review. We have the following request for information:

1. Clarify the primary efficacy endpoint used in Studies C97-208, C97-225, and I97-200. Describe the spirometry testing procedure performed during the study visits, including the timing of the testing in relation to study drug administration and whether trough FEV1 values were obtained.

Please submit a response by COB January 11, 2010, via email to Eunice.Chung@fda.hhs.gov. The official response should be submitted to the NDA shortly after as well. If you have any questions, please contact Eunice Chung, Regulatory Project Manager, at 301-796-4006.

Drafted by: SLimb/23DEC2009
Initialed by: Sbarnes/23DEC2009
 SSeymour/23DEC2009

Finalized by: Echung/23DEC2009

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

12/23/2009



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

FACSIMILE TRANSMITTAL SHEET

DATE: December 22, 2009

To: Michael Belman, Director, Global Regulatory Affairs	From: Eunice Chung, Pharm.D.
Company: Schering Plough Research Institute	Division of Pulmonary and Allergy Drug Products
Fax number: Secure Email	Fax number: 301-796-9728
Phone number: 908-740-4997	Phone number: 301-796-2300

Subject: NDA 22-518 Information Request #4

**Total no. of pages including
cover:**2

Comments:

Document to be mailed: YES xNO

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Your submission, dated May 21, 2009, to NDA 22-518, is currently under review. We have the following comments/requests for information:

1. Provide the method used and a summary of validation data for analysis of [REDACTED]^{(b) (4)} (including for example, the limit of detection, among other data) as a potential leachable in the drug product.

The following comments pertain to your September 4, 2009 amendment:

2. Provide an agreement to maintain specifications (i.e., a list of tests, acceptance criteria and test methods) in NDA 22-518 for each of the two drug substances. (Comment 9)
3. Provide graphical comparisons of the updated 18 and 24 month stability data for the additional stability batches, with earlier data for the additional stability batches as well as with all of the primary stability data. Include both individual data and mean data in the graphs. Include proposed acceptance criteria in the graphs. (Comment 11)

The following comments pertain to your November 25, 2009 amendment (in response to our Information Request dated October 26, 2009):

4. Since the safety assessment of foreign particulates in the drug product is based upon the highest mass of particulates for a batch [REDACTED]^{(b) (4)} and since your analytical method determines foreign particles by number not by mass, clarify the assumptions that you used to obtain the mass of the foreign particulates. (Comment 5)
5. In your previously reported characterization of the drug product cleaning procedure, you have indicated that “the results demonstrate that the DCU data for the dry wipe regime are comparable with the control group (not cleaned) DCU data, for both drug substances.” In view of this, clarify what is the cause of the difference in APSD performance in inhalers returned from the clinic, when patient-used actuators were compared with new actuators. (Comment 7)
6. United States Pharmacopeia/National Formulary and the United States Homeopathic Pharmacopoeia are the drug compendia officially recognized in the United States. Provide a copy of the current EP method for [REDACTED]^{(b) (4)} impurities. Indicate whether there is a USP General Chapter method for control of specific [REDACTED]^{(b) (4)} impurities [REDACTED]^{(b) (4)} that could substitute for the EP method. (Comment 11)
7. Add a [REDACTED]^{(b) (4)} acceptance criterion to the specification for the throat and mouthpiece adaptor stage grouping, since the mass of drugs deposited on this stage grouping is substantial and it should be consistent. (Comment 16a)

Please provide a response by COB January 4, 2010. An official submission to the NDA should follow. If you have any questions, please contact Eunice Chung, Pharm.D., Regulatory Project Manager, at 301-796-4006.

Drafted by: ASchroeder/December 18, 2009

Initialed by: Prasad Peri/December 18, 2009
Sandy Barnes/December 20, 2009

Finalized by: EChung/December 22, 2009

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

12/22/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO: <i>(Division/Office)</i> Dr. Jean Wu, DPAP/OND			FROM: Alan C. Schroeder, Ph.D.	
DATE: 11/30/2009	IND NO.:	NDA NO.: 22518	TYPE OF DOCUMENT: Original NDA	DATE OF DOCUMENT: 5/22/2009
NAME OF DRUG: Dulera Inhalation Aerosol (mometasone furoate & formoterol fumarate dihydrate)		PRIORITY CONSIDERATION: S	CLASSIFICATION OF DRUG: 3 (new dosage form) and/or 4 (new combination)	DESIRED COMPLETION DATE: 12/3/09
NAME OF APPLICANT:				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY _____		<input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT		<input type="checkbox"/> REPOSENSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (<i>Specify below</i>) – evaluate safety of leachables, impurities, degradants, etc. in drug product.
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH	
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER			<input type="checkbox"/> CHEMISTRY <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER	
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> <i>IN-VIVO</i> WAIVER REQUEST	
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY			<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (<i>List below</i>)	
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL	
COMMENTS/SPECIAL INSTRUCTIONS (<i>Attach additional sheets if necessary</i>)				
<p>Please see the attached consult request for pharm/tox assessment of degradation products, leachables, and foreign particulates in the drug product N22-518, which was e-mailed to Dr. Tim Robison on October 22, 2009. It is repeated here as an official consult request, in order that it may be documented in DARRTS.</p>				
SIGNATURE OF REQUESTER			METHOD OF DELIVERY <i>Check one</i> <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> DARRTS	
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER	

Consult request for pharm/tox assessment of degradation products, leachables, and foreign particulates in the drug product N22-518:

Please evaluate the safety of the following information for drug product leachables, degradants, and foreign particulates, for maximum levels in the drug product:

See non-clinical overview in the original NDA for more details of the following impurities (section 2.4).

(b) (4)

(b) (4)

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/

ALAN C SCHROEDER
11/30/2009

PRASAD PERI
11/30/2009



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

Memorandum of Facsimile Correspondence

Date: 26OCT2009

To: Michael Belman
Director, Global Regulatory Affairs

Company: Schering Plough Research Institute

Fax: N/A - Secure Email

Phone: 908-740-4997

From: Eunice Chung, Pharm.D.
Regulatory Management Officer
Division of Pulmonary and Allergy Products

Subject: NDA 22-518

of pages: 2

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Thank you.

We are currently reviewing your New Drug Application, submitted on May 21, 2009, for Dulera. We have the following requests:

1. This pertains to your leachables stability study beginning on page 24 of section 3.2.P.2.4 of the NDA. You have indicated on page 25 that in this study you have identified (b) (4) leachable compounds. You have provided information on (b) (4) of them which are indicated to have exceeded their respective limits of quantitation. For the other (b) (4) identified leachables, it is not clear whether their limits of quantitation are above the AET limits. Provide information pertaining to the other (b) (4) identified leachables and indicate whether any of them are above the AET and the SCT (according to the PQRI proposal). Explain if any of these (b) (4) are considered part of the (b) (4) unspecified leachables, and if not, why not.
2. Provide a succinct clarification of the specific control strategies and the extractable limits for leachables present above the PQRI SCT (b) (4) and specify who performs the tests. (b) (4). Express the extractables limits both in amount per component, and amount per canister.
 (b) (4)
4. This pertains to data tables from the placebo stability study of leachables (examples of this include the data in Tables 9 through Table 38 on pages 44-64 of section P.2.4.). Indicate whether the extractables data are mean data, or the highest observed individual data, and whether they are representative of multiple batches in each case. Provide (b) (4) extractables data for the batches of valves or valve components used for your placebo stability study of leachables (Tables 41 and 42, pg. 70). Indicate whether (b) (4) is soluble in the formulation.
5. Provide an example calculation of the total mass of the foreign particulates (e.g. for Table 2, page 85, section 3.2.P.2.4) and provide available information about the identities of the approximately (b) (4) of particles that were not (b) (4) (b) (4)
6. This pertains to your patient simulation study, beginning on page 379 of section 3.2.P.2.4 of the NDA. It appears that there are an unusual number of results that are (b) (4) the acceptance criteria for DCU, especially for the 100/5 mcg strength (batch GIB037) in the second half of the canister life. Some outliers are substantially (b) (4) for the product. Provide an explanation for these results and indicate what assurance you have that they are not typical results

(if they are not typical results) for this drug product. Provide an explanation for

(b) (4)

7. Provide an explanation of the substantial tendency towards (b) (4) particle sizes in the drug suspension, in samples of drug product returned from the clinic, compared to controls, 25°C/60%RH stability data and temperature cycling data (from the -2°C to 40°C study).
8. Provide side by side comparative data of the spray pattern data, comparing drug product returned from clinical studies with other drug product data (e.g., batch analyses).
9. Provide the actual results and conclusion of your investigations of each drug product sample that was returned with a complaint from clinical studies (Section P.2.4). The general, generic conclusions that you have provided (e.g., pp. 524-528) do not provide an understanding of the situation for individual complaint samples.
10. This pertains to Section P.4.2. Provide an agreement to utilize a different laboratory (other than that of the manufacturer) to periodically verify the information on the supplier's certificate of analysis for HFA 227.
11. This pertains to Section P.4.4. Provide adequate justification for the individual fatty acid specifications which control these impurities in the oleic acid excipient, or reduce the maximum limits in the specification for certain specified fatty acids to levels more consistent with the data (b) (4).
For these examples, the individual maximum limit exceeds the highest data point by (b) (4). Provide methods validation/verification data for European Pharmacopeia method 2.4.22(C) (Composition of Fatty Acids by Gas Chromatography) including, among other attributes, the limits of detection and limits of quantitation for this method.
12. The following comments pertain to Section P.5.2 of the NDA:
 - a. Clarify if the "Unit Spray Collection Apparatus" is identical to the apparatus described in USP <601>. (This pertains to test method (b) (4))
 - b. Clarify the process of selecting an actuator for the Aerodynamic Particle Size Distribution test and for the Dose Content Uniformity tests. It is the Agency's expectation that the actuator packaged with the filled canister

should be used for performance testing of the drug product. (This pertains to test method (b) (4))

- c. Clarify the calibration procedure for the instrument used in the analytical procedure (b) (4)

13. The following comments pertain to Section P.5.3 of the NDA:

- a. Provide representative chromatograms for the impurity and degradation product methods to illustrate specificity.
- b. Provide illustrations of the “reprocessing” of data following the update or change of analytical procedures for the drug product (one example is the change from (b) (4) Clarify how the validation report for (b) (4) applies as well to (b) (4)
- c. Clarify that the ability of the method to quantify potential levels of unspecified known degradation products (for formoterol fumarate) in the drug product specification (controlled to NMT (b) (4) has been validated for accuracy in the Analytical Procedures (b) (4) and (b) (4) for, since the validation report for these procedures (pg. 17) states that accuracy was assessed “for all other known FF related impurities” at the quantitation limit of (b) (4)

14. The following comment pertains to Section P.5.4 of the NDA: “Provide detailed illustrations of the “reprocessing” of data following the update or change of analytical procedures for the drug product (one example is the change from (b) (4)

15. The following comments pertain to Section P.5.5 of the NDA.

- a. Provide acceptance criteria containing (b) (4) significant figures for specified mometasone furoate degradants.
- b. Modify the acceptance criterion for individual unspecified degradation products of mometasone furoate to be (b) (4) for consistency.
- c. Add a drug product specification for individual unspecified degradants of formoterol fumarate.

16. The following comments pertain to Section P.5.6 of the NDA:

- a. (b) (4)

NDA 22-518
Dulera
Schering Plough

(b) (4)

- b. Provide an agreement to reevaluate the drug product APSD specifications after a reasonable amount of stability data for additional batches is available, after approval of this NDA.
 - c. Provide an agreement to reevaluate the degradation product specifications for the drug product after a reasonable amount of stability data for additional batches is available, after approval of this NDA.
17. Provide comparative summary data to demonstrate the dose proportionality of APSD on a stage by stage basis.
18. (b) (4)

Please provide a response to me by COB November 20, 2010 via secure email (Eunice.Chung@fda.hhs.gov) or via fax (301-796-9728). If you have any questions, please me at 301-796-4006.

Eunice H. Chung, Pharm.D.
Regulatory Management Officer

NDA 22-518
Dulera
Schering Plough

Drafted: Eunice Chung/23OCT2009
Initialed: Sandy Barnes/23OCT2009
Alan Schroeder/23OCT2009
Prasad Peri/23OCT2009

Finalized: Eunice Chung/26OCT2009

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

10/26/2009



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

Memorandum of Facsimile Correspondence

Date: 13 OCT 2009

To: Michael Belman
Director, Global Regulatory Affairs

Company: Schering Plough Research Institute

Fax: N/A - Secure Email

Phone: 908-740-4997

From: Eunice Chung, Pharm.D.
Regulatory Project Manager
Division of Pulmonary and Allergy Products

Subject: NDA 22-518 IR

of pages: 2

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Thank you.

NDA 22-518
Dulera
Schering Plough

We are currently reviewing your New Drug Application, submitted on May 21, 2009, for Dulera. We have the following requests:

The New Drug Application references USP regarding the performance of microbial limits testing. However, provide the following:

1. The test methods which are used for performing microbial limits.
2. Data demonstrating that the microbial limits test methods are suitable for use with the subject drug product. Reference is made to USP<61> which states in part, "The ability of the test to detect microorganisms in the presence of product to be tested must be established".

Please provide a response to me by November 13, 2009 via secure email (Eunice.Chung@fda.hhs.gov) or via fax (301-796-9728). If you have any questions, please me at 301-796-4006.

Eunice H. Chung, Pharm.D.
Regulatory Management Officer

NDA 22-518
Dulera
Schering Plough

Drafted: EChung/5OCT2009
Initialed: SBarnes/8OCT2009
John Metcalfe/13OCT2009
Stephen Langille/2OCT2009

Finalized: EChung/13OCT2009

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

10/13/2009

REQUEST FOR CONSULTATION

TO (Office/Division): **Microbiology Team**

FROM (Name, Office/Division, and Phone Number of Requestor): **Eunice H. Chung, RPM ext 64006**

DATE September 16, 2009	IND NO.	NDA NO. 22-518	TYPE OF DOCUMENT original NDA submission	DATE OF DOCUMENT May 22, 2009
NAME OF DRUG Dulera		PRIORITY CONSIDERATION S	CLASSIFICATION OF DRUG Respiratory	DESIRED COMPLETION DATE December 15, 2009

NAME OF FIRM: **Schering Plough**

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

- | | |
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| <input type="checkbox"/> PRIORITY P NDA REVIEW
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> CONTROLLED STUDIES
<input type="checkbox"/> PROTOCOL REVIEW
<input type="checkbox"/> OTHER (SPECIFY BELOW): | <input type="checkbox"/> CHEMISTRY REVIEW
<input type="checkbox"/> PHARMACOLOGY
<input type="checkbox"/> BIOPHARMACEUTICS
<input type="checkbox"/> OTHER (SPECIFY BELOW): |
|---|--|

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION
<input type="checkbox"/> BIOAVAILABILITY STUDIES
<input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE
<input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS
<input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|--|--|

IV. DRUG SAFETY

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

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: This is a formal microbiology consult request for review of the relevant micro information for NDA 22-518. This would include at least the following in the original NDA:

Microbial challenge study (section 3.2.P.2.5)

Microbial limits specifications (drug product) in section 3.2.P.5.1

Microbial limits analytical procedure in section 3.2.P.5.2 (referenced only to USP)

Microbial limits results under "batch analyses" (section 3.2.P.5.4)

Microbial limits (section 3.2.P.5.6) under "justification of specifications"

Microbial limits analytical procedure under "Stability Data" (section 3.2.P.8.3)

Validation of microbial limits method (under "Stability Data" (section 3.2.P.8.3)

Stability summary (under "Stability Data" part 4.10, page 475, section 3.2.P.8.3)

Stability data tables (under "Stability Data" part 5.9, beginning on page 1594, section 3.2.P.8.3)

The NDA is electronically accessible via DARRTS. Please contact me with any questions. Once a reviewer is assigned, please notify me.

Thank you

SIGNATURE OF REQUESTOR

Eunice Chung, Pharm.D., RPM

METHOD OF DELIVERY (Check one)

DFS

EMAIL

MAIL

HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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

09/16/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 70,283
NDA 22-518

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Schering Corporation
2000 Galloping Hill Road
Kenilworth, New Jersey 07033

Attention: Susan Yule
Senior Manager, Global Regulatory Affairs

Dear Ms. Yule:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act and your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Mometasone Furoate and Formoterol Fumarate Inhalation Aerosol, [REDACTED] ^{(b) (4)} 100 mcg/5 mcg, and 200 mcg/5 mcg.

We also refer to your IND submission dated March 13, 2009, correspondence, received March 16, 2009, requesting review of your proposed proprietary name, Dulera. We have completed our review of the proposed proprietary name, Dulera and have concluded that it is acceptable.

The proposed proprietary name, Dulera, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your March 13, 2009, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sean Bradley, R.Ph., Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-1332. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
IND 70283	ORIG 1		FORMOTEROL FUMARATE/MOMETASONE FUROATE

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/s/

CAROL A HOLQUIST
08/12/2009



NDA 22-518

FILING COMMUNICATION

Schering Plough
2000 Galloping Hill Road
Kenilworth, NJ 07033-0530

Attention: Michael Belman
Director, Global Regulatory Affairs

Dear Mr. Belman:

Please refer to your new drug application (NDA) dated May 21, 2009, received May 22, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Dulera (mometasone furoate/formoterol fumarate) Inhalation Aerosol (b) (4), 100/5 and 200/5 microgram.

We also refer to your submissions dated June 4, and June 16, and July 1, and July 24, 2009.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is March 22, 2010.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by the February 10, 2010 Labeling Teleconference.

During our filing review of your application, we identified the following potential review issues:

Clinical:

1. The adequacy of the data to support (b) (4) separate proposed dose levels will be a review issue. Upon preliminary review, the application lacks a direct comparison of the (b) (4) MF/F 200/10 mcg dose levels, making justification of each dose

level more difficult.

2. The definition for asthma exacerbation used as the co-primary endpoint in the pivotal studies [REDACTED] (b) (4).
[REDACTED]
[REDACTED] Supportive secondary endpoints, such as the trough FEV1, will be of particular interest.
3. Preliminary review of the program indicates that there is no replicate data demonstrating [REDACTED] (b) (4). As noted in the pre-NDA meeting, the level of efficacy and safety data expected for each of the monotherapy products in your combination program is comparable to an individual drug product in development for product registration. Whether the submitted data meets this standard will be a review issue.
4. The adequacy of your application to support the safety of your product will be a review issue. Given the December 2008 Pulmonary Allergy Drugs Advisory Committee meeting regarding the safety of long-acting beta agonists, the safety database required for new products containing long-acting beta agonists is under active discussion within the Agency. Upon preliminary review, we have concerns that your safety database may not be adequate to address the safety signals discussed during the advisory committee meeting, such as asthma hospitalizations, serious asthma exacerbations, and asthma-related death.

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:

Clinical:

1. Clarify whether the pivotal Phase 3 trials used an MDI device with a dose counter and whether dose counter data was collected during the trials. Provide the total number of devices used in the phase 3 trials and indicate the number/percentage of devices with dose counters.

Clinical Pharmacology:

2. The validation method cannot be located in clinical pharmacology studies. Submit the information or provide the location of the method.

3. Justify the reason for not obtaining PK samples in adolescents in the pivotal Phase III trials.

Statistics:

4. For all Phase 3 Datasets: In the datasets and appropriate documentation text 'Define.pdf' for variable SAEXREAS in the SAEX and SAEX1st datasets, break down reasons for diagnosing severe asthma exacerbation by FEV₁, PEF_R, emergency treatment by doctor, hospitalization, or rescue with restricted drugs such as systemic corticosteroids, beta-adrenergic bronchodilators, ipratropium bromide, cromolyn sodium, tiotropium, theophylline, etc. outside of emergency treatment and hospital. If possible list the restricted drug taken. Where SAEXREAS = 'MULT,' provide the list of reasons for each event. You may choose to provide this information either by supplementing the SAEX and SAEX1st datasets or by adding a new dataset.
5. For all Phase 3 Datasets: Provide unabridged FEV₁ data up to and beyond relative time 000000+ for all studies, either by supplementing the VISIT and VISITN datasets or by providing additional datasets. Ensure that one of the categories included is non-locf.
6. For all Phase 3 Datasets: Explain why there are generally eight values for WKSTATUS in dataset GOALN per week for each patient.
7. For all Phase 3 Datasets: Ensure that all codings employed are carefully documented, and ensure that your documentation is unambiguous. For example, in the document 'define.pdf' define codes 4 and 5 for variable METHOD1 and code 88 for variable VISIT in all AUC and AUCN datasets, define code value 3 for variable WKSTATUS in dataset GOALN, define codes 1, 3, and 5 used for time in the PROP_N datasets, codes for variable CTG_{TX}T in dataset LABINVC, etc.
8. For all Phase 3 Datasets: Clarify in the appropriate documentation text 'Define.pdf' for the AUC and AUCN datasets whether LOCF in the label for variable METHOD1 refers to LOCF for FEV₁ within visits, LOCF for AUC between visits, or both. Where the value of variable METHOD1 = 2, clearly define what is meant by 'Base,' and where METHOD1 = 0, clearly define what is meant by 'Raw.' Provide, clearly label, and clearly define non-locf data for FEV₁ and AUC. For example, in study P04073 dataset AUCN no data variable is clearly labeled to indicate it is non-locf.

Chemistry, Manufacturing and Controls:

9. Identify updates and changes in the CMC information for mometasone furoate and formoterol fumarate, since approval of the referenced NDAs for these drug substances. Provide full drug substance specifications (acceptance criteria and analytical procedures) for each drug substance and specify acceptance testing performed on receipt of the drug substances, as well as test data accepted on a certificate of analysis to NDA 22-518.

Attach structural formulas of the drug substance and all organic impurities to the specification sheets.

10. Provide side by side comparative performance data (full profile of APSD and Emitted Dose) for the individual and mean values (including standard deviation) for the combination product versus the monotherapy products (mometasone furoate MDI and formoterol fumarate MDI). This information may be provided graphically and in a tabular form. Clarify if the monotherapy product formoterol fumarate MDI was formulated in the HFA 227. If not, illustrate the challenges in developing this HFA 227 formulation and using it as a monotherapy comparator in Phase 3 clinical trials. If there are pharmaceutical differences (APSD and Emitted Dose) in the performance aspects of the combination product and monotherapy products, interpretation of the results obtained in the clinical trials might be difficult if not impossible. The differences cannot be easily attributable to the drug product. Provide the approximate time of manufacture and time of testing for the samples used in the performance testing mentioned above.
11. Update the NDA with real time stability data (e.g., 18 months and 24 months) for the additional stability batches.
12. Clarify the drug product characterization studies were carried out with drug product that underwent the stabilization process.

Labeling:

13. Address the following issues/deficiencies with regard to format and re-submit by August 15, 2009. This updated version of the labeling will be used for further labeling discussions.

- a. 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)
(b) (4) in patients 12 years of age and older.”

Full Prescribing Information: “DULERA is indicated... (b) (4) treatment of asthma, (b) (4), in adults and children 12 years of age and older.”

- b. Be more specific with your reference numbers in the Highlights section:
 - i. Under 1st bullet in the Contraindications section, change the reference number to 4 to 4.1.
 - ii. Under the 2nd bullet in the Contraindications section, change the reference

number from 4 to 4.2.

- iii. Provide a reference number for the information in the Adverse Events section.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

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.

We acknowledge your request for a waiver of the requirement that the **Highlights** of Prescribing Information be limited to no more than one-half page. We will consider your request during labeling discussions. In the meantime, we encourage you to submit revised labeling that meets the half page requirement.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver and a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver and/or the partial deferral request are denied.

If you have any questions, call Eunice H. Chung, Regulatory Project Manager, at (301) 796-4006.

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 A CHOWDHURY
08/04/2009



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

Memorandum of Facsimile Correspondence

Date: 20 JULY2009

To: Michael Belman
Director, Global Regulatory Affairs

Company: Schering Plough Research Institute

Fax: N/A - Secure Email

Phone: 908-740-4997

From: Eunice Chung, Pharm.D.
Regulatory Project Manager
Division of Pulmonary and Allergy Products

Subject: NDA 22-518

of pages: 2

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

If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 796-2300 and return it to us at FDA, 10903 New Hampshire Ave, Building 22, DPAP, Silver Spring, MD 20993.

Thank you.

NDA 22-518
Dulera
Schering Plough

We are currently reviewing your New Drug Application, submitted on May 21, 2009, for Dulera. We have the following requests:

1. Clarify if Astellas Pharma, Japan does the release and stability testing for the unmiconized formoterol fumarate. Contact the DMF holder and identify all formoterol fumarate testing sites (release and stability) used for the Schering NDA.
2. Clarify if Novartis does the stability and release testing for the micronized formoterol fumarate.

Please provide a response to me by COB Friday, July 24, 2009 via secure email (Eunice.Chung@fda.hhs.gov) or via fax (301-796-9728). If you have any questions, please me at 301-796-4006.

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

NDA 22-518
Dulera
Schering Plough

Drafted: EChung/17JULY2009
Initialed: SBarnes/17JULY2009
Alan Schroeder/17JULY2009
Prasad Peri/17JULY2009
Ali Al-Hakim/17JULY2009

Finalized: EChung/20JULY2009

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/s/

Eunice Chung
7/20/2009 07:58:53 AM
CSO



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

Memorandum of Facsimile Correspondence

Date: 15JUN2009

To: Susan Yule
Senior Manager and Liason

Cc: Michael Belman
Director, Global Regulatory Affairs

Company: Schering Plough Research Institute

Fax: N/A - Secure Email

Phone: 908-740-5847
908-740-4997

From: Eunice Chung, Pharm.D.
Regulatory Project Manager
Division of Pulmonary and Allergy Products

Subject: NDA 22-518

of pages: 2

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If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 796-2300 and return it to us at FDA, 10903 New Hampshire Ave, Building 22, DPAP, Silver Spring, MD 20993.

Thank you.

NDA 22-518
Dulera
Schering Plough

We are currently reviewing of your New Drug Application, submitted on May 21, 2009.
We have the following requests:

1. Please clarify the testing sites listed in each form 356h. Identify what types of manufacturing, packaging, and testing they perform (e.g., release testing, stability testing, microbial testing, in process testing, extractables and leachables testing, labeling etc.).
2. Provide updated letters of authorization to the appropriate DMFs for the manufacture of both drug substances.

Please provide a response to me by Thursday, June 18, 2009. If you have any questions, please me at 301-796-4006.

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

NDA 22-518
Dulera
Schering Plough

Drafted: EChung/11JUN2009
Initialed: SBarnes/11JUN2009
Prasad Peri/15JUN2009
Ali Al-Hakim/15JUN2009

Finalized: EChung/15JUN2009

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/s/

Eunice Chung
6/15/2009 02:29:29 PM
CSO

REQUEST FOR CONSULTATION

TO (Office/Division): **Office of Surveillance and Evaluation**

FROM (Name, Office/Division, and Phone Number of Requestor): **Eunice H. Chung, RPM, Division of Pulmonary and Allergy Products, 301 796 4006**

DATE
June 8, 2009

IND NO.

NDA NO.
22-518

TYPE OF DOCUMENT
NDA

DATE OF DOCUMENT
May 22, 2009

NAME OF DRUG
**Dulera
(mometasone/formoterol)**

PRIORITY CONSIDERATION
S

CLASSIFICATION OF DRUG
Respiratory

DESIRED COMPLETION DATE
October 14, 2009

NAME OF FIRM: **Schering Plough**

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

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|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

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| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

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

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Dear OSE, this consult is for the review of a new electronic for NDA 22-518 (available at the following address in the EDR: \\CDSESUB1\EVSPROD\NDA022518\0000 as well as in module 1.14 in Global Summit Review). Please review the labeling (Highlights, Full Prescribing Information, Medication guide and canister- and carton-container labels). PDUFA date is 3/22/2010; MidCycle Meeting is 10/21/2010

SIGNATURE OF REQUESTOR
Eunice H. Chung

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/

Eunice Chung

6/8/2009 01:58:38 PM

REQUEST FOR CONSULTATION

TO (Office/Division): **Division of Drug Marketing, Advertising and Communications (DDMAC)**

FROM (Name, Office/Division, and Phone Number of Requestor): **Eunice H. Chung, RPM, Division of Pulmonary and Allergy Products, 301 796 4006**

DATE June 8, 2009	IND NO.	NDA NO. 22-518	TYPE OF DOCUMENT NDA	DATE OF DOCUMENT May 22, 2009
NAME OF DRUG Dulera (mometasone/formoterol)		PRIORITY CONSIDERATION S	CLASSIFICATION OF DRUG Respiratory	DESIRED COMPLETION DATE October 14, 2009

NAME OF FIRM: **Schering Plough**

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

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|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

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

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Dear DDMAC, this consult is for the review of a new electronic NDA 22-518 (available at the following address in the EDR: \\CDSESUB1\EVSPROD\NDA022518\0000 as well as in module 1.14 in Global Summit Review). Please review the labeling (Highlights, Full Prescribing Information, Medication guide and canister- and carton-container labels).
PDUFA date is 3/22/2010; MidCycle Meeting is 10/21/2010

SIGNATURE OF REQUESTOR
Eunice H. Chung

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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

/s/

Eunice Chung

6/8/2009 02:00:57 PM

Chung, Eunice

From: Hamilton-Stokes, Deveonne
nt: Tuesday, June 02, 2009 5:06 PM
to: Chung, Eunice
Cc: Bradley, Sean; Bridges, Todd; Toyer, Denise P; Holquist, Carol A; Jenkins, Darrell; Chowdhury, Badrul A; Raggio, Miranda
Subject: 90 Day email for IND 70,283 Dulera
Attachments: Dulera 90 day email chart 2.doc

Hello Eunice,

This email is to notify you that the Division of Medication Error Prevention and Analysis (DMEPA) has completed the assessment of the proposed proprietary name Dulera (Mometasone furoate/formoterol fumarate dihydrate). DMEPA will allow the use of the name Dulera for this product.

Please share this information with your team and notify us whether you concur or do not concur with our assessment and if you have any concerns regarding the proposed proprietary name. We would be willing to meet with the Division to discuss this analysis, if needed. Please respond with any comments within 14 days of receipt of this communication.

Attached are tables that summarize our analysis.



Dulera 90 day email
chart 2.do...

Thank you,

veonne

Deveonne Hamilton-Stokes, RN, BSN
LCDR USPHS
Division of Medication Errors Prevention and Analysis
FDA OSE
10903 New Hampshire Blvd
Silver Spring, MD 20993
Building 22 Room 4413
Phone: (301) 796-2253
Fax: (301) 796-9865
deveonne.hamilton-stokes@fda.hhs.gov

Appendix C:

CDER Prescription Study Responses

Outpatient Prescription	Voice Prescription	Inpatient Medication Order
Dulera	Dulera	Dulera
Dulera	Dulara	Dulera
Duleron	Dulara	Dulera
Dulera		Dulexa
Dulera		

Appendix D: Names without convincing look-alike and/or sound-alike similarities to Dulera.

Proprietary Name	Similarity to Dulera
Dulcolax	Look
Dilantin	Look
Dilaudid	Look

Appendix E: Identified foreign product name

Proprietary Name	Similarity to Dulera	Country
Dolana (Tramadol)	Look	Indonesia
Dolaren (Diclofenac)	Look	Mexico

Appendix F: Proprietary names not approved by the Agency or withdrawn from Agency prior to approval

Proprietary Name	Similarity to Dulera	Status
(b) (4)		

***This document contains proprietary and confidential information that should not be released to the public.

Appendix G: Products with limited or no additional information found in DMEPA References 1-16

Proprietary Name	Similarity to Dulera	Additional Information
Dolorex (Acetaminophen/Salicylamide/ Phenyltoloxamine)	Look/Sound	None
Delaro	Look/Sound	USPTO- Listed as Dead Trademarks for: Chemical Preparation for the treatment of seeds and fertilizer and Educational Services
Doloro	Look/Sound	USPTO-Listed as Dead Trademark for an analgesic preparation
Bois Douleur	Look	Natural medicine states it is a small evergreen tree in which the roots, bark and fruits are used to treat various conditions. Tree is found in the Pacific Islands, Asia, Australia and India

Appendix H: Products with no numerical overlap in strength or dose.

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)
Dulera (Mometasone furoate/formoterol fumarate dihydrate)		Inhalation aerosol (metered dose inhaler) ^{(b) (4)} 100/5 mcg, 200/5 mcg	2 puffs every 12 hours (morning and evening)
Duloxetine Hydrochloride	Look	Capsule : 20 mg, 30 mg, 60 mg	Range depending on condition being treated from 20 mg twice daily to 60 mg once daily
Pylera (Bismuth Subcitrate Potassium; Metronidazole; Tetracycline)	Look	Capsule : 140 mg/125 mg/125 mg	3 capsules taken 4 times a day, after meals and at bedtime for 10 days. One omeprazole 20 mg capsule should be taken twice a day with Pylera after the morning and evening for 10 days
Clolar (clofarabine)	Look	Injection: 20 mg/20 mL	52 mg/m ² as an intravenous infusion over 2 hours daily for 5 consecutive days of a 28 day cycle. Repeat every 2 to 6 weeks
Debrase (Debridase)	Look	Topical Gel: 2 g, 5 g	Apply to wound surface
Debrox	Look	Otic drops: none	Instill 5 to 10 drops twice daily for up to 4 days
Clobex (Clobetasol Propionate)	Look	Topical Shampoo: 0.05% Topical Spray 0.05%	Apply to scalp once a day in a thin film to the affected areas; leave in place for 15 minutes, then add water, lather and rinse Spray directly onto the affected skin areas twice daily and rubbed in gently and completely
Exubera (Insulin Recombinant Human)	Look	Inhalation Powder: 1 mg, 3 mg	Individualized and determined based on the physician's advice in accordance with the needs of the patient
Dolene (Propoxyphene Hydrochloride)	Look	Capsule: 65 mg	65 mg every 4 hours
Covera-HS (Verapamil Hydrochloride)	Look	Tablet: 180 mg, 240 mg	Initiate therapy at 180 mg and dose may be titrated up to 480 mg once daily at bedtime
Lutera (Ethinyl estradiol/Levonorgestrel)	Sound	Tablet: 20 mcg/0.1 mg	One white tablet daily for 21 consecutive days, followed by one peach inert tablet daily for seven consecutive days
^{(b) (4)}			

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)
Dulera (Mometasone furoate/formoterol fumarate dihydrate))		Inhalation aerosol (metered dose inhaler) (b) (4) 100/5 mcg, 200/5 mcg	2 puffs every 12 hours (morning and evening)
Alera (Hydroquinone)	Look/Sound	Topical emulsion: 4%	Apply to the affected area twice daily
Stelara*** (Ustekinumab)	Look/Sound	Solution for injection autoinjector : 45 mg, 90 mg	45 mg or 90 mg subcutaneously followed by an additional dose 4 weeks after the first dose, then every 12 weeks thereafter.
Dolorac (Capsaicin)	Look	Topical lotion/cream	Apply to affected area up to four times daily
Aldara (Imiimod)	Sound	Topical cream: 5%	Apply to the affected area two, three or five times per week (depending on condition being treated) for up to 16 weeks
Dilacor XR (Diltiazem Hydrochloride)	Look	Capsule: 120 mg, 180 mg, 240 mg	180 mg to 480 mg once daily
Leukeran (Chlorambucil)	Look	Tablet: 2 mg	0.1 to 0.2 mg/kg of body weight daily for three to six weeks (typically amounts to 4 mg to 10 mg per day for the average patient)
Relera (Chlorpheniramine/ Phenylephrine)	Look/Sound	Caplets: 8 mg/20 mg	One caplet 2 to 3 times per day
Del-Vi-A (Vitamin A Palmitate) Discontinued, but generics available	Look	Capsule: 50,000 units	Individualized to patient

Appendix I: Products with numerically similar strength or achievable dose with differentiating product characteristics

Product name with potential for confusion	Similarity to Product Name	Strength	Usual Dose	Other Differentiating Product Characteristics
Dulera (Mometasone furoate/formoterol fumarate dihydrate)		MDI: (b) (4) 100/5 mcg, 200/5 mcg	2 puffs every 12 hours (morning and evening)	
Alora (Estradiol)	Look/ Sound	Patch: 0.05 mg, 0.075 mg, 0.1 mg, 0.025 mg	Apply 0.05 mg to 0.025 mg twice weekly	Dosage forms: Inhalation aerosol (metered dose inhaler) vs. Patch Frequency of administration: Every 12 hours vs. twice weekly Route of administration: Oral inhalation vs. Topical Instructions for use: 2 puffs vs. Apply XX mg Additionally, although the products have numerically similar strengths 25/5 mg vs. 0.025 mg, the preceding zeros in 0.025 mg helps to elongate and provide distinction between those strengths.
Soliris (Eculizumab)	Look	Injection: 300 mg vial	600 mg every 7 days for the first 4 weeks, followed by 900 mg for the fifth dose 7 days later, then 900 mg every 14 days thereafter	Dosage forms: Inhalation aerosol (metered dose inhaler) vs. Injection Frequency of administration: Every 12 hours vs. 7 days to 14 days Route of administration: Oral inhalation vs. Intravenous Usual dose: 2 puffs vs. 600 mg or 900 mg
Femara (Letrozole)	Sound	Tablet: 2.5 mg	One tablet once a day	Dosage forms: Inhalation aerosol (metered dose inhaler) vs. Tablet Frequency of administration: Every 12 hours vs. once a day Route of administration: Oral inhalation vs. oral Usual dose: 2 puffs vs. 1 tablet Due to the fact that Femara is a single strength product, the strength may be omitted.

Product name with potential for confusion	Similarity to Product Name	Strength	Usual Dose	Other Differentiating Product Characteristics
Dulera (Mometasone furoate/formoterol fumarate dihydrate)		MDI: (b) (4) 100/5 mcg, 200/5 mcg	2 puffs every 12 hours (morning and evening)	
Dilor, Dilor 400 (Dphylline) Discontinued, but generics available	Look/ Sound	Tablet: 200 mg , 400 mg	15 mg/kg up to 4 times a day (about six hours apart)	Dosage forms: Inhalation aerosol (metered dose inhaler) vs. Tablet Frequency of administration: Every 12 hours vs. 4 times a day (about six hours apart) Route of administration: Oral inhalation vs. oral Usual dose: 2 puffs vs. 15 mg/kg Additionally, Dilor is dosed based on body weight.
Dolorex Forte (Acetaminophen/ Hydrocodone)	Look/ Sound	Tablets: 500 mg/5mg	1 to 2 tablets every 4 to 6 hours as needed for pain	Dosage forms: Inhalation aerosol (metered dose inhaler) vs. Tablet Frequency of administration: Every 12 hours vs. every 4 to 6 hours Route of administration: Oral inhalation vs. oral Additionally, Dolorex Forte is a single strength product and thus the strength will likely be omitted on an order.
Fludara (Fludarabine)	Sound	Injection: 50 mg vial	25 mg/m ² administered intravenously over a period of approximately 30 minutes daily for five consecutive days. Each 5 day course of treatment should commence every 28 days	Dosage forms: Inhalation aerosol (metered dose inhaler) vs. Injection Frequency of administration: Every 12 hours vs. 5 consecutive days every 28 days Route of administration: Oral inhalation vs. Intravenous Usual dose: 2 puffs vs. 25 mg/m ²

Appendix J: Potential confusing name with numerical overlap in strength or dose

Failure Mode: Name Confusion	Causes (could be multiple)	Rationale
<p>Dulera (Mometasone furoate/formoterol fumarate dihydrate) MDI <small>(b) (4)</small></p> <p>100/5 mcg, 200/5 mcg</p>		<p>Usual Dose: 2 puffs every 12 hours (morning and evening)</p>
<p>Sular (Nisoldipine extended-release tablets) 8.5 mg, 17 mg, 25.5 mg, 34 mg</p> <p>17 mg to 34 mg once daily</p>	<p>Orthographic similarity: both names share similar letters in similar positions “uler” vs. “ular” and capital letter “D” may look like capital letter “S” when scripted.</p> <p>Numerically similar strength (25/5 mg and 25.5 mg)</p>	<p>Although Dulera and Sular share a numerically similar strength strength, differentiating product characteristics will help reduce the risk of medication errors. Sular is available as a tablet with a usual dose of one tablet per day. In contrast, Dulera is a metered dose inhaler and the usual dose is 2 puffs every 12 hours. These directions will be included in an order for Dulera or it can be written as “use as directed”. However, Sular is less likely to be written as “use as directed”. Therefore the directions for use will help distinguish these products.</p>



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type: B

Meeting Category: Pre-NDA

Meeting Date and Time: December 15, 2008

Meeting Location: Building 22, Room 1417

Application Number: 70283

Product Name: mometasone furoate/formoterol fumarate MDI

Received Briefing Package: November 14, 2008

Sponsor Name: Schering-Plough

Meeting Requestor: Susan Yule, Senior Manager, Global Regulatory Affairs

Meeting Chair: Badrul A. Chowdhury, M.D., Ph.D.

Meeting Recorder: Miranda J. Raggio, R.N., B.S.N., M.A.

Meeting Attendees:

FDA Attendees:

- Badrul A. Chowdhury, M.D., Ph.D., Division Director, Division of Pulmonary and Allergy Products
- Lydia Gilbert-McClain, M.D., Deputy Director, Division of Pulmonary and Allergy Products
- Sally Seymour, M.D., Deputy Director for Safety, Division of Pulmonary and Allergy Products
- Anthony Durmowicz, M.D., Clinical Team Leader, Division of Pulmonary and Allergy Products
- Susan Limb, M.D., Medical Reviewer, Division of Pulmonary and Allergy Products
- Tim Robison, Ph.D., Acting Pharmacology/Toxicology Supervisor, Division of Pulmonary and Allergy Products
- Wei Qiu, Ph.D., Acting Clinical Pharmacology Team Leader, Division of Clinical Pharmacology II, Office of Clinical Pharmacology
- Partha Roy, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II, Office of Clinical Pharmacology

Prasad Peri, Ph.D., Pharmaceutical Assessment Lead, Division of Pre- Marketing Assessment I, Branch I

Alan Schroeder, Ph.D., CMC Reviewer, Division of Pre-Marketing Assessment I, Branch II

Qian Li, Sc.D., Biostatistics Team Leader, Office of Biostatistics, Division of Biometrics II

Feng Zhou, Ph.D., Biostatistics Reviewer, Office of Biostatistics, Division of Biometrics II

Miranda Raggio, Regulatory Project Manager, Division of Pulmonary and Allergy Products

Sponsor Attendees: Hendrik Nolte, Clinical Research, Schering-Plough
Heribert Staudinger, Clinical Team, Schering-Plough
Davis Gates, Biostatistics, Schering-Plough
Teddy Kosoglou, Early Clinical Research and Experimental Medicine, Schering-Plough
David De Sousa, Global Regulatory Affairs, Schering-Plough
Robert Kowalski, VP for N. America and Japan Global Affairs, Schering-Plough
Greg Howe, Global Regulatory Affairs (CMC), Schering-Plough
Gretchen Trout, Global Regulatory Affairs, Schering-Plough
Kati Picone, Global Regulatory Affairs, Schering-Plough
Susan Yule, Global Regulatory Affairs, Schering-Plough
Prakash Navaratnam, Global Health Outcomes, Schering-Plough
Ann Shea, Drug Regulatory Affairs, Novartis
Mark E. Lloyd, Clinical Research, Novartis

BACKGROUND

Schering-Plough requested a Type B Pre-NDA meeting in correspondence dated October 22, 2008, received October 23, 2008. The purpose of this meeting was to discuss the proposed NDA for a newly developed fixed dose combination product, mometasone furoate/formoterol fumarate metered dose inhaler. The meeting package was submitted to the Division on November 13, 2008. Upon review of the meeting package, the Division provided responses to Schering-Plough via telephone facsimile on December 11, 2008. The content of the telephone facsimile is printed below, with the Division's responses in *bold italics* and the Schering-Plough questions in normal font. In an email

dated December 12, 2008, Schering-Plough notified the Division that they would like to discuss questions 1, 11a, 11b, 12b, and 13 at the face-to-face meeting.

Summary comments of the meeting discussion are found in *italics* following the each question.

QUESTIONS AND RESPONSES

Question 1: Does the Agency agree that, pending a satisfactory review of the data, the proposed nonclinical and clinical studies adequately support an NDA for the proposed indication?

Division Response: *No, we do not agree. Based on the limited information provided in the briefing package, we have concerns about the completeness of your development program. In particular, we are concerned about the adequacy of the data to support the use of the monotherapy comparators included in the two pivotal efficacy and safety studies. We have the following comments regarding your development plan:*

(b) (4)

From a nonclinical standpoint, your program appears adequate to support an NDA.

Question 2: Does the Agency agree that, pending a satisfactory review of the data, the proposed safety database adequately supports an NDA for the proposed indication?

Division Response: *Yes, we agree.*

Discussion: *No further discussion occurred.*

Question 3: Does the Agency agree with the proposed criteria for submitting CRFs and annotated CRFs?

Division Response: *Yes, the proposed criteria are acceptable.*

Discussion: *No further discussion occurred.*

Question 4: Does the Agency agree that the overall content and format of the NDA, as presented in the draft Table of Contents, is acceptable?

Division Response: *Yes, your proposal is acceptable. We refer you to the "Guidance for Industry: Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product"*

Applications and Related Submissions Using the eCTD Specifications (October, 2005) for further information on the eCTD format.

Discussion: *No further discussion occurred.*

Question 5: Does the Agency agree with the proposed cross referencing to existing NDAs for the monotherapy components?

Division Response: *Yes, the proposed cross-referencing is acceptable.*

Discussion: *No further discussion occurred.*

Question 6: Does the Agency agree with the proposed format for data submission and accompanying documents for the individual study datasets?

Division Response: *Yes, the proposed format is acceptable.*

Discussion: *No further discussion occurred.*

Question 7: Does the Agency agree with the proposal that pharmacokinetic data from clinical pharmacology studies are not included in the NDA?

Division Response: *No, we do not agree. The PK concentration data, as well as derived PK parameter data (summary tables, individual listings and PK datasets) from all clinical pharmacology studies, must be included at the time of initial NDA submission.*

Discussion: *No further discussion occurred.*

Question 8: Does the Agency agree with the tabular format and selection of efficacy endpoints proposed in the sample tabulations?

Division Response: *Yes, the proposed tabulations are acceptable.*

Discussion: *No further discussion occurred.*

Question 9: Does the Agency agree with the proposed format and content of the individual tables for safety, and the proposal to pool Phase 3 safety data and present the Phase 1 and 2 studies separately?

Division Response: *Yes, the proposed format and pooling strategies are acceptable.*

Discussion: *No further discussion occurred.*

Question 10: Does the Agency have any additional comments regarding the proposed pediatric clinical development plan, including the request for a deferral and waiver?

Division Response: *Decisions regarding requests for deferral and waiver are made at the time of NDA approval. The Division has no other comments at this time.*

Discussion: *No further discussion occurred.*

Question 12a: If appropriate validation of the seven-item Asthma Control Questionnaire is prepared and presented for all relevant age groups using the draft guidance for industry “Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims,” does the Agency agree with the Sponsor’s approach to measure improvement in asthma control using the seven-item ACQ as a key secondary endpoint in the MF/F combination studies?

Division response: *Yes, your plan to use the ACQ as a key secondary endpoint is acceptable.*

Discussion: *No further discussion occurred.*

ADDITIONAL COMMENTS

Pharmacology/Toxicology

1. Any impurities exceeding ICH recommended qualification threshold as per ICH Guidances Q3A(R) and Q3B(R) will need to be qualified. The maximum allowable daily dose for each genotoxic and structural alert impurity is (b) (4), unless the impurity has been toxicologically qualified. Genotoxic impurities that are structurally similar and would be expected to interact with DNA in a similar manner, however, should be added up for a total amount that does not exceed (b) (4). Extractables and leachables with no structural alerts that exceed (b) (4) (qualification threshold) will need to be qualified.

Discussion: Schering-Plough stated that this issue will be addressed in the NDA submission.

Biostatistics

- 2. Include all SAS programs for the efficacy analyses and efficacy analysis data sets created in your NDA submission.***

Discussion: No further discussion occurred.

Clinical Pharmacology

- 3. Clarify whether your adult/adolescent clinical development program has any PK assessment of MF and formoterol in the adolescent population (12-17 years of age). Based on the proposed pediatric clinical development plan described in Appendix 7 of your briefing package, it is unclear whether you have incorporated all the changes recommended at our January 30, 2008, meeting. Specifically, it is not clear if you are conducting steady-state PK assessment of both active ingredients in the pediatric patient population as part of the Phase 3 program.***

Discussion: Schering-Plough confirmed that PK assessment of MF and formoterol in the adolescent population was not done. Schering-Plough stated it is anticipated that approximately 10 percent of the Phase 3 study population (~200 patients) will be in the 12-17 age range, in other words, efficacy and safety data will be available for this group and that should triumph any systemic exposure assessment in this age-group. The Division stated that this will be viewed as a data gap and therefore encouraged Schering to address this issue in the NDA submission. Schering also pointed out that they will have other measures of systemic exposure without getting in to the details of what they are.

Schering-Plough confirmed that they were following the recommendations of the FDA made in the January 30, 2008, meeting.

ADDITIONAL DISCUSSION POINTS

The Division notified Schering-Plough that due to the December 10-11th Advisory Committee meeting regarding LABAs, the response provided to Question 2 of this Briefing Package may no longer stand. Additional safety data for both the adult and adolescent populations may be required. Schering acknowledged this point.

- 1. The Division stated that with regard to LABAs and ICS, the FDA as an agency needs to regroup internally and determine what kind of safety data will be required for children, adolescents, and adults. It is anticipated that there will be a significantly higher standard for safety data.*
- 2. The Division stated that the question of what benefit a combination product will provide over steroids alone will be looked at in depth.*
- 3. Schering asked the Division if it was anticipated that the proposed NDA for the mometasone furoate/formoterol fumarate MDI would go to an Advisory Committee (AC). The Division responded that this determination will be made at the time of the NDA submission, and that the timing of the submission will play a large part in determining the need for an AC.*

4. The Division asked if Schering had a target date for the NDA submission. Schering responded that they plan to submit the NDA for MF/MF MDI mid-2009.

Drafted by: Miranda Raggio/December 15, 2008

Initialed by:

Partha Roy/December 16, 2008

Qian Li/December 18, 2008

Wei Qiu/December 19, 2008

Tim Robison/December 17, 2008

Susan Limb/December 22, 2008

Sally Seymour/December 22, 2008

Lydia Gilbert-McClain/January 2, 2009

Finalized by: Miranda Raggio/January 2, 2009

Linked Applications

Sponsor Name

Drug Name / Subject

IND 70283

SCHERING CORP

FORMOTEROL
FUMARATE/MOMETASONE FUROATE

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

/s/

MIRANDA B RAGGIO

01/02/2009



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

FACSIMILE TRANSMITTAL SHEET

DATE: December 11, 2008

To: Susan Yule, Senior Manager Global Regulatory Affairs	From: Miranda Raggio, RN, BSN, MA Regulatory Project Manager
Company: Schering-Plough	Pulmonary and Allergy Products Email: Miranda.Raggio@fda.hhs.gov
Fax number: 1-908-740-2243	Fax number: 301-796-9728
Phone number: 1-908-740-5847	Phone number: 301-796-2109
Subject: IND 70283 Meeting Comments	

Total no. of pages including cover: 5

Comments: Please call or send an email to confirm receipt. Thanks, miranda

Document to be mailed: YES xxNO

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

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2109. Thank you.

Attached are the FDA responses (in ***bold italics***) to your questions in the November 13, 2008, meeting package regarding IND 70,283. You have the option of canceling our meeting of December 15, 2008, if these answers are clear to you. If you choose to have this meeting, we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, nor reach agreement on, such changes at the meeting. Any modifications to the development plan, for which you would like FDA feedback, should be submitted as a new meeting request.

Please let me know as soon as possible if you would like to cancel the meeting or change it to a teleconference.

QUESTIONS AND RESPONSES

Question 1: Does the Agency agree that, pending a satisfactory review of the data, the proposed nonclinical and clinical studies adequately support an NDA for the proposed indication?

Division Response: No, we do not agree. Based on the limited information provided in the briefing package, we have concerns about the completeness of your development program. In particular, we are concerned about the adequacy of the data to support the use of the monotherapy comparators included in the two pivotal efficacy and safety studies. We have the following comments regarding your development plan:



From a nonclinical standpoint, your program appears adequate to support an NDA.

Question 2: Does the Agency agree that, pending a satisfactory review of the data, the proposed safety database adequately supports an NDA for the proposed indication?

Division Response: *Yes, we agree.*

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Division Response: *Yes, the proposed cross-referencing is acceptable.*

Question 6: Does the Agency agree with the proposed format for data submission and accompanying documents for the individual study datasets?

Division Response: *Yes, the proposed format is acceptable.*

Question 7: Does the Agency agree with the proposal that pharmacokinetic data from clinical pharmacology studies are not included in the NDA?

Division Response: *No, we do not agree. The PK concentration data, as well as derived PK parameter data (summary tables, individual listings and PK datasets) from all clinical pharmacology studies, must be included at the time of initial NDA submission.*

Question 8: Does the Agency agree with the tabular format and selection of efficacy endpoints proposed in the sample tabulations?

Division Response: *Yes, the proposed tabulations are acceptable.*

Question 9: Does the Agency agree with the proposed format and content of the individual tables for safety, and the proposal to pool Phase 3 safety data and present the Phase 1 and 2 studies separately?

Division Response: *Yes, the proposed format and pooling strategies are acceptable.*

Question 10: Does the Agency have any additional comments regarding the proposed pediatric clinical development plan, including the request for a deferral and waiver?

Division Response: Decisions regarding requests for deferral and waiver are made at the time of NDA approval. The Division has no other comments at this time.



Question 12a: If appropriate validation of the seven-item Asthma Control Questionnaire is prepared and presented for all relevant age groups using the draft guidance for industry "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims," does the Agency agree with the Sponsor's approach to measure improvement in asthma control using the seven-item ACQ as a key secondary endpoint in the MF/F combination studies?

Division response: Yes, your plan to use the ACQ as a key secondary endpoint is a acceptable.



ADDITIONAL COMMENTS

Pharmacology/Toxicology

1. Any impurities exceeding ICH recommended qualification threshold as per ICH Guidances Q3A(R) and Q3B(R) will need to be qualified. The maximum allowable daily dose for each genotoxic and structural alert impurity is (b) (4) unless the impurity has been toxicologically qualified. Genotoxic impurities that are structurally similar and would be expected to interact with DNA in a similar manner, however, should be added up for a total amount that does not exceed (b) (4). Extractables and leachables with no structural alerts that exceed (b) (4) (qualification threshold) will need to be qualified.

Biostatistics

2. Include all SAS programs for the efficacy analyses and efficacy analysis data sets creation in your NDA submission.

Clinical Pharmacology

3. Clarify whether your adult/adolescent clinical development program has any PK assessment of MF and formoterol in the adolescent population (12-17 years of age).

Based on the proposed pediatric clinical development plan described in Appendix 7 of your briefing package, it is unclear whether you have incorporated all the changes recommended at our January 30, 2008, meeting. Specifically, it is not clear if you are conducting steady-state PK assessment of both active ingredients in the pediatric patient population as part of the Phase 3 program.

Please contact Miranda Raggio, Senior Regulatory Project Manager, at 301-796-2109 with any questions.

IND 70283

Drafted by: Miranda Raggio/December 8, 2008
Sandy Barnes/December 8, 2008
Initialed by: Feng Zhou/December 9, 2008
Partha Roy/December 9, 2008
Qian Li/December 9, 2008
Wei Qiu/December 9, 2008
Tim Robison/December 9, 2008
Susan Limb/December 8, 2008
Sally Seymour/December 9, 2008
Badrul Chowdhury/December 11, 2008
Finalized by: Miranda Raggio/December 11, 2008

Linked Applications

Sponsor Name

Drug Name

IND 70283

SCHERING CORP

FORMOTEROL
FUMARATE/MOMETASONE FUROATE

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

/s/

MIRANDA B RAGGIO
12/11/2008



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

Meeting Type: Type C
Meeting Category: IND meeting/Other
Meeting Date and Time: April 23, 2008, 3:00-4:30pm
Meeting Location: Teleconference
Application Number: IND 70,283
Product Name: mometasone furoate/formoterol fumarate metered dose inhaler
Received Briefing Package February 25, 2008
Sponsor Name: Schering Corporation/Novartis
Meeting Requestor: Schering Corporation
Meeting Chair: Badrul A. Chowdhury, M.D., Ph.D, Division Director
Meeting Recorder: Lori Garcia, R.Ph., Senior Regulatory Management Officer

Meeting Attendees:

FDA Attendees

Badrul A. Chowdhury, M.D., Ph.D, Division Director, Division of Pulmonary and Allergy Products
Sally Seymour, M.D., Medical Team Leader, Division of Pulmonary and Allergy Products
Lori Cantin, R.Ph., Sr. Regulatory Management Officer, Division of Pulmonary and Allergy Products
Prasad Peri, Ph.D., Pharmaceutical Assessment Lead, Office of New Drug Quality Assessment
Alan Schroeder, Ph.D., CMC Reviewer, Office of New Drug Quality Assessment
Ching-Long J. Sun, Ph.D., Pharm/Tox Team Leader, Division of Pulmonary and Allergy Products
Tim Robison, Ph.D., Pharm/Tox Reviewer, Division of Pulmonary and Allergy Products

Schering Corporation

Michael Mitchell, Ph.D., Vice President, Oral & Respiratory Product Development
Diane Zezza, Ph.D., Vice President, Global Regulatory Affairs - CMC
Robert Alekel, Director, Global Regulatory Affairs - CMC
Greg Howe, Senior Manager & Liaison, Global Regulatory Affairs - CMC

Susan Yule, Senior Manager, Global Regulatory Affairs
Gretchen Trout, Director, Regulatory Relations and Policy
Jill Sherwood, Ph.D., Senior Principal Scientist, Respiratory Product
Development
Brent Donovan, Ph.D., Associate Director, Analytical Development
Caesar Snodgrass-Pilla, Associate Director, Analytical Development
Nicholas Montefusco, Director, Technology Transfer
Aleksander Zuyev, Manager, Device Development
Neil Johnson Ph.D, FRCPATH, Senior Fellow, Toxicology

Novartis

Ann Shea, Senior Associate Director, Drug Regulatory Affairs
Barbara Haeberlin, Ph.D., Project Leader, Inhalation & Device Development

1.0 BACKGROUND

Schering/Novartis submitted a meeting request dated February 25, 2008, for a Type C meeting to discuss your mometasone furoate/formoterol fumarate metered dose inhaler product.

A briefing package for this meeting was submitted on February 25, 2008. Upon review of the briefing package, the Division responded to Schering/Novartis' questions via fax on April 21, 2008. The content of that fax is printed below. A teleconference was held on April 23, 2008. Any discussion that took place at the meeting is captured directly under the relevant original response including any changes in our original position. Schering/Novartis' questions are in ***bold italics***; FDA's responses are in *italics*; discussion is in normal font.

2.0 QUESTIONS, FDA RESPONSES, and MEETING DISCUSSION

2.1 QUESTION 1

Does the Agency Agree that the data presented here adequately addresses the (b) (4) concerns raised at our CMC Guidance Meeting on Sept. 12, 2006, and supports (b) (4) as an appropriate step in the routine manufacturing process?

FDA Response:

- a. *We acknowledge that upon the recommendation of the Agency, you have conducted an investigation of the cause/mechanism of (b) (4). (b) (4) As indicated by the Agency, the process may be acceptable pending the strength of the scientific justification for the process. Your evaluation of the problem seems to be appropriate in the types of testing that were conducted, however, our assessment will depend on a full review of the data to be provided in your future NDA.*

b. Note that the scientific rationale provided in your briefing package should be included in the pharmaceutical development section of your future NDA.

c. In your future NDA, clarify the mechanism by which (b) (4)

Discussion

Schering/Novartis clarified that the mechanism of (b) (4)

(b) (4) Schering/Novartis asked if this explanation was acceptable for the future NDA submission. The FDA stated that it was looking for a rationale as to why (b) (4) and confirmed that this is the type of discussion that should be included in the NDA.

2.2 QUESTION 2

Does the Agency agree that the proposed (b) (4) for this product is acceptable?

FDA Response:

Your proposal is acceptable.

2.3 QUESTION 3

Does the Agency concur with the proposed approach to correlation, which is based on PQRI recommendations, where:

(b) (4)

FDA Response:

From a CMC perspective we will accept the approach outlined in the PQRI recommendation for extractables and leachables in orally inhaled and nasal drug products for the correlation between extractables and leachables. From the pharmacology/toxicology perspective, the evaluation will be an NDA review issue.

2.4 QUESTION 4

Does the Agency concur with the approach proposed for the (b) (4)

FDA Response:

We concur with the overall approach (b) (4)
(b) (4) and to perform a toxicological evaluation of the maximum levels observed. It is premature for us to agree on specifications at this time.

2.5 QUESTION 5

Does the Agency concur that (b) (4)

FDA Response:

We will perform a CMC and pharmacology/toxicology evaluation of the results of your investigation into the source and amounts of (b) (4) in the drug product when you submit your NDA. It is premature for us to discuss the issue of drug product specifications for (b) (4) at this time.

2.6 QUESTION 6

Does the Agency concur with the proposed approach to (b) (4) (b) (4)

FDA Response:

- a. This is a review issue that will be evaluated in consultation with the pharmacology/toxicology reviewers during the NDA review period.
- b. Your proposal assumes that the toxicity profiles of (b) (4).
- c. Clarify how you plan to account for (b) (4).

Discussion

Schering/Novartis explained that the (b) (4)

Schering/Novartis stated that they did not feel that additional testing is warranted, and asked if this was acceptable to the FDA. The FDA stated that the explanation seems reasonable, but is a review issue, and that Schering/Novartis should provide justification for this in the future NDA.

2.7 QUESTION 7

Does the Agency concur with

FDA Response:

Schering/Novartis asked if this is the information that FDA was looking for, and FDA answered affirmatively. The justification of (b) (4) should be provided to the future NDA.

(b) (4)

Discussion

Schering/Novartis asked if (b) (4) could be submitted in an annual report. The FDA agreed that an annual report would be acceptable, presuming that there was no data suggesting any differences between (b) (4)

2.8 QUESTION 8

Does the Agency agree to the proposed strategy for submission of (b) (4)

FDA Response:

a. Y our proposed submission strategy is reasonable.

(b) (4)

Discussion

Schering/Novartis stated that:

(b) (4)

- they plan to demonstrate via a toxicological assessment that these higher exposure levels are not of toxicological concern.

Schering/Novartis asked the FDA if this approach was acceptable. The FDA stated that the approach seems reasonable.

- c. *Your justification for the characterization studies to be provided in the supplement will be an NDA review issue.*

2.9 QUESTION 9

Does the Agency agree with the clinical return testing plan as outlined above?

FDA Response:

Your proposal is acceptable as long as your testing protocol incorporates drug product units (b) (4). We also remind you that all malfunctioning drug product units reported during the clinical trials should also be evaluated relative to the specific patient complaints, and the results of the investigation reported in the NDA.

3.0 ADDITIONAL COMMENTS FOR YOUR FUTURE NDA

- 1. Include a well documented Pharmaceutical Development Report as per the ICH-Q8 guideline, and highlight how critical quality attributes and critical process parameters are identified and controlled.*
- 2. At the beginning of the CMC section, include a table of all facilities (including contract manufacturers/testers etc. for drug substance and drug product) Include the function of each facility, the contact name and address, the CFN number, and the complete name and address of the facility.*

Discussion

Schering/Novartis noted that the NDA submission would be electronic and asked if it would be acceptable to include this data in Module 1.1.2. The FDA stated that this was acceptable, as long as the data is consistent with Modules 2 and 3.

- 3. Ensure that all of the above facilities are ready for inspection by the day the application is submitted, and include a statement confirming this in the NDA cover letter.*
- 4. Provide tabular summaries of your stability data, organized by test parameter, and separated by manufacturing site, batch, storage condition and container closure system. Provide graphical summaries of any trending stability data, organized by test parameter, including mean and individual data.*

5. Provide specifications for leachables in the drug product, whether or not an extractable/leachable correlation is established. If the Agency concurs that an appropriate extractable/leachables correlation has been established, then it may be possible to delete routine leachables testing in the drug product and place a footnote in the specification sheet, indicating that leachables are not routinely tested because of the control of extractables in appropriate container closure components.

4.0 ACTION ITEMS

No action items were identified during the meeting.

If you have any questions, call LCDR Lori Cantin, Senior Regulatory Management Officer, at (301) 796-1212.

Drafted: LGarcia/5.7.08

Initialed: AAIHakim/5.12.08
ASchroeder/5.12.08
TRobison/5.12.08
CSun/5.12.08
SSeymour/5.12.08
BChowdhury/5.15.08

Finalized: LGarcia/May 16, 2008

Linked Applications

Sponsor Name

Drug Name

IND 70283

SCHERING CORP

FORMOTEROL
FUMARATE/MOMETASONE FUROATE

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/s/

LORI G Cantin
05/16/2008



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

Meeting Type: Type C
Meeting Category: IND meeting/Other
Meeting Date and Time: January 30, 2008, 12:00-1:30pm
Meeting Location: Teleconference
Application Number: IND 70,283
Product Name: mometasone furoate/formoterol fumarate metered dose inhaler
Received Briefing Package December 21, 2007
Sponsor Name: Schering Corporation
Meeting Requestor: Schering Corporation
Meeting Chair: Badrul A. Chowdhury, M.D., Ph.D, Division Director
Meeting Recorder: Lori Garcia, R.Ph., Senior Regulatory Management Officer

Meeting Attendees:

FDA Attendees

Badrul A. Chowdhury, M.D., Ph.D, Division Director, Division of Pulmonary and Allergy Products
Sally Seymour, M.D., Acting Deputy Director, Division of Pulmonary and Allergy Products
Susan Limb, M.D., Clinical Reviewer, Division of Pulmonary and Allergy Products
Lori Garcia, R.Ph., Regulatory Management Officer, Division of Pulmonary and Allergy Products
Sandra Suarez, Ph.D., Clinical Pharmacology Reviewer, Office of Clinical Pharmacology 2
Wei Qiu, Ph.D., Clinical Pharmacology Team Leader, Office of Clinical Pharmacology 2
Qian Li, Ph.D., Biostatistics Team Leader, Division of Biometrics II
Ted Guo, Ph.D., Biostatistics Reviewer, Division of Biometrics II

Schering Corporation

Dr Heribert Staudinger
Dr Davis Gates
Dr Hendrik Nolte
Dr Michael Belman
Dr Temitayo Ajayi

Dr Kathryn Picone
Gretchen Trout
David De Sousa
Dr Teddy Kosoglou
Susan Yule

Novartis

Ann Shea
Dr Chad Orevillo
Dr Cheryl Lassen
Dr Linda Armstrong

1.0 BACKGROUND

Schering/Novartis submitted a meeting request dated October 29, 2007, for a Type C meeting to discuss the proposed pediatric clinical development program for the fixed dose combination product, mometasone furoate/formoterol fumarate metered dose inhaler.

A briefing package for this meeting was submitted on December 21, 2007. Upon review of the briefing package, the Division responded to Schering/Novartis' questions via fax on January 28, 2008. The content of that fax is printed below. A teleconference was held on January 30, 2008. Any discussion that took place at the meeting is captured directly under the relevant original response including any changes in our original position. Schering/Novartis' questions are in *bold italics*; FDA's responses are in *italics*; discussion is in normal font.

2.0 GENERAL COMMENTS AND DISCUSSION

(b) (4)

5.0 ACTION ITEMS

No action items were identified during the meeting.

If you have any questions, call LCDR Lori Garcia, Senior Regulatory Management Officer, at (301) 796-1212.

Drafted: LGarcia/2.22.08

Initialed: QLi/2.26.08 & 2.27.08
WQui/2.26.08
SSuarez/2.25.08
SSeymour/2.26.08 & 2.27.08
SLimb/2.26.08
BChowdhury/2.28.08

Finalized: LGarcia/2.28.08

Linked Applications

Sponsor Name

Drug Name

IND 70283

SCHERING CORP

FORMOTEROL
FUMARATE/MOMETASONE FUROATE

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/s/

LORI A GARCIA
02/28/2008

MEMORANDUM OF MEETING MINUTES

MEETING DATE: November 3, 2004
TIME: 2:00pm-3:00pm
LOCATION: 5600 Fishers Lane
Rockville, MD 20857
APPLICATION: PIND 70,283
DRUG NAME: mometasone furoate/formoterol fumarate
TYPE OF MEETING: PIND

MEETING RECORDER: Lori Garcia

FDA ATTENDEES:

Division of Pulmonary and Allergy Drug Products

Badrul A. Chowdhury, M.D., Ph.D., Division Director
Tejashri Purohit-Sheth, M.D., Clinical Reviewer
Richard Lostritto, Ph.D., Chemistry Team Leader
Emmanuel O. Fadiran, Ph.D., Clinical Pharmacology/Biopharmaceutics Team Leader
Shinja Kim, Ph.D., CPBP Reviewer
Lori Garcia, R.Ph., Regulatory Project Manager
Sue Jane Wang, Ph.D., Acting Biostatistics Team Leader

EXTERNAL CONSTITUENT ATTENDEES:

Schering

Teddy Kosoglou, Pharm.D., Group Director, Clinical Pharmacology
Herbert Staudinger, M.D., Vice President, Clinical Research
David De Sousa, Senior Director, Global Regulatory Affairs
Michael Belman, Regulatory Fellow, Global Regulatory Affairs
Gretchen Trout, Director, Regulatory Relations and Policy
Carole Schumann, Associate Director, Project Management
Robert Alekel, Global Regulatory Affairs, CMC
Michael Mitchell, CMC
Joel Sequeira, CMC

Novartis

Ann Horowitz, Assoc. Director, Exploratory Clinical Director
Andre Van As, M.D., Ph.D., Executive Director, Global Regulatory Section Head
Ann Shea, Associate Director, Drug Regulatory Affairs
Jill Horowitz, Director, Project Leader, Respiratory Therapeutic Area

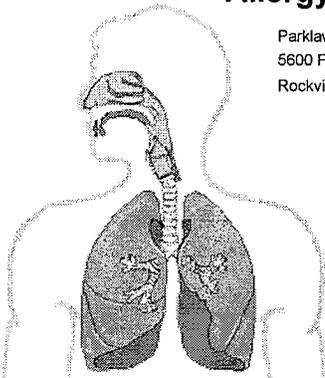
BACKGROUND:

A type C clinical pharmacology/clinical guidance Pre-IND meeting request was received on August 11, 2004. The meeting package was received on October 6, 2004. The package was reviewed and the Divisions responses and comments were forwarded to Schering on November 1, 2004, for review prior to the meeting. Schering/Novartis were given the option to cancel the meeting if the responses were clear. Schering/Novartis decided to continue with the meeting as scheduled to discuss/clarify the Division's responses.

DISCUSSION:

Slide 1

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Allergy Drug Products**



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10/26/04

PIND 70,283

1

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Slide 2

PIND 70,283
Mometasone/Formoterol
Schering/Novartis

Tejashri Purohit-Sheth, MD.
Pre-IND Meeting
03 November 2004

Slide 3

1. The combination product under development will be an HFA-227 pressurized metered-dose inhaler. However, it is noted that both mometasone furoate and formoterol fumarate are commercially available and extensively characterized in dry powder inhaler forms. The sponsors feel that the marketed dry powder inhalers are the appropriate reference controls for clinical pharmacology and clinical studies where comparison of the combination versus components is required. Does the Agency agree?

- No, we do not agree. Ideally, the comparison of the combination product to each of its individual components should be made to the individual components of the same formulation.
- However, if you are unable to develop the individual components of the combination in the same formulation as the proposed combination product, then you need to evaluate the pharmaceutical differences between the two formulations.
 - If the two formulations (HFA MDI and dry powder) are not pharmaceutically distinct, then it may be possible to use the dry powder formulations as the individual comparators for the combination HFA MDI.

• CMC Response to Question 1

- Dry Powder formulations are considered distinct from MDI formulations
- Provide appropriate CMC bridging data to establish pharmaceutical comparability which support clinical comparisons.

10/26/04 PIND 70,263 4

Schering/Novartis noted that they are unable to develop medicinal components in the same formulation as the proposed combination product. They requested clarification as to why the Division does not agree that the marketed mometasone furoate (MF) and formoterol fumarate (FF) dry powder inhaler (DPI) products are appropriate reference controls for comparison to the HFA-227 pressurized metered dose inhaler combination MF/FF product. Schering/Novartis stated that the 2 drug substances in the combination product are the same drug substances present in the mono products. (b) (4)

[Redacted]

[Redacted]

[Redacted] (b) (4)

[Redacted]

[Redacted]

[Redacted] Their

intent is to confirm the effectiveness of the combination product clinically and that they would like to understand the Division's conceptual concern regarding their use of an MDI combination product. They feel that the clinically relevant comparators are the DPI

products. Once the mono-product comparators are shown to be similar to the combination product, then it would be a matter of a “switch” program.

The Division stated that the issue is not a matter of a “switch” program, but of a program demonstrating that the combination product is better than each of the individual components. Ideally, to do so, the formulations/devices of the combination product should be similar to the mono-product comparators. However, the Division recognizes the sponsor’s difficulty in producing MDI mono-product comparators, and recognizes the challenge in linking DPI and MDI products based on PSD. Nonetheless, the sponsor needs to provide CMC data to demonstrate pharmaceutical comparison between the combination MDI product and the DPI mono-products.

[REDACTED] (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] (b) (4)

[REDACTED] (b) (4)

[REDACTED]

The effect of each component of the combination product would need to be demonstrated, independent of the effect of the formulation.

Slide 5

5. Asthma treatment guidelines (NHLBI 1997, GINA 2002) do not recommend the use of long-acting β_2 -agonists without concurrent administration of inhaled corticosteroids. In this context the sponsors propose not to include long-acting β_2 -agonist only arms into studies which would otherwise evaluate the combination versus its components, and to compare the combination only to a mometasone arm. Does the Agency agree with their proposed approach?

- No, we do not agree. To satisfy the requirements of the Combination Rule, you must demonstrate that each individual component contributes to the efficacy of the combination product.
- Therefore, your phase III development plan and this proposed study should include at a minimum a combination product arm, a mometasone arm, and a formoterol arm.

10/26/04 PIND 70,283 5

Schering/Novartis agreed to include a formoterol arm in their clinical studies.

Slide 6

- **CMC Response to Question 5.**
 - Provide appropriate CMC bridging data to support the pharmaceutical comparability of each mono-therapy formulation (MDI or DPI) to that of the proposed combination product

10/26/04 PIND 70,263 6

Schering/Novartis asked for further clarification of what constitutes “appropriate CMC bridging to support clinical comparison between MDI and DPI’s.” The Division stated that we would need CMC data to support that the products are the same or how they are different, and that a clarification of the differences between the products would be needed if the products are identified as pharmaceutically distinct. The Division stated that Schering/Novartis would have to link the two product classes clinically and show that MDI or DPI effects don’t come into play. The Division noted that it would be a challenging issue and a developmental risk. (b) (4)

Division stated that they would be open to reviewing proposals submitted and would provide feedback if requested.

Schering/Novartis agreed that CMC characterization is important, but stated that they believe that clinical performance is more relevant. Additionally, Schering/Novartis proposed that the most relevant comparison for physicians would be against the marketed

DPIs, rather than MDI mono products developed only for comparative studies. The Division stated that for FDA's review, we would need to evaluate the contribution of each active component independent of formulation effects. The Division suggested that successful comparison to component MDIs made available for study would be a logical way to proceed, and would address this CMC issue.

Schering/Novartis indicated that they would like a second pre-IND meeting in the second quarter of 2005 to review their full program. The Division noted that, in general, only one pre-IND meeting is granted. A request for a second pre-IND meeting could be submitted and would be evaluated at that time.

Slide 7

6. Since Protocol P04073 will be conducted in patients with moderate persistent asthma and both mometasone furoate specifically and ICAS in general have established efficacy in asthma, the sponsors believe that a comparison vs. placebo is neither in the best interest of the patients enrolled, nor required to ascertain the superiority of the combination over its ICS component. Therefore the sponsors propose that no placebo arm be required in P04073. This study is then simply a comparison of the combination against mometasone furoate alone. Does the Agency agree with their approach?

- With respect to the lack of a placebo arm, to satisfy the requirements of the Combination Rule a placebo arm is not necessarily a requirement.
- However, should you develop HFA formulations of the individual components for comparisons with the combination product as stated in response #1 then you will need to include a placebo arm in your studies.
- If you are able to use the dry powder formulations as the comparator individual components of the combination product (i.e. by demonstrating that they are pharmaceutically the same), then a placebo may not be necessary.

10/26/04 PIND 70,283 7

Additional Comments

- Study 2101, a study in asthmatics, is stated to be the first study.
 - However, the combination product should first be given to healthy volunteers prior to proceeding to asthmatics.

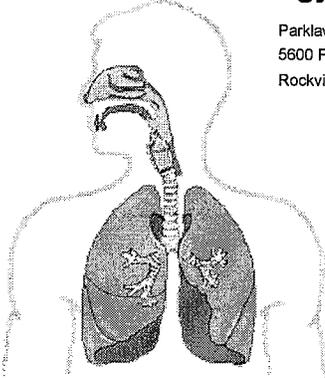
10/26/04 PIND 70,283 9

The Division elaborated on this rationale for this comment, stating that it was advisable to study a new formulation in healthy volunteers to rule out any issues related to the

formulation. The Division noted that, for example, the proposed combination product contains oleic acid, which is not part of the formulation of the mono DPI products.

Slide 10

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10/26/04

PIND 70,283

10

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Slide 11

Pre-IND 70283
Formoterol/Mometasone HFA MDI
Schering-Plough and Novartis

Clinical Pharmacology and
Biopharmaceutics

Shinja Kim, Ph.D.

Slide 12

Question 2: The sponsors propose that the clinical safety data from the two phase I studies 2101 and 2102 and the pharmacodynamic data from Study 2101 are sufficient to characterize the new fixed dose combination MDI prior to commencing phase 2/3 trials, given the existing information available for the two active components, formoterol fumarate (via Aerolizer®) and mometasone furoate (via Twisthaler®), administered individually. Additionally, the sponsors propose that these studies sufficiently characterize the new combination MDI relative to the marketed DPIs to enable using the marketed DPIs for individual component control arms in Phase 3. Does the Agency agree?

Comment: We agree.

10/26/04 PIND 70,283 12

Slide 13

Question 3:
The sponsors propose that a total clinical pharmacology program consisting of four phase I studies (studies 2101, 2102, 2104, and 2105) adequately characterizes the PK, component interaction, dose proportionality, PD, and systemic (extrapulmonary) effects of the formoterol fumarate/mometasone furoate 5/100 and 5/200 fixed dose combination MDIs. Does the Agency agree?

Comment:
 (b) (4)

10/26/04 PIND 70,283 13

Schering/Novartis stated that they understood and agreed with Division's comment to Question 3.

Slide 14

Question 4:
The HPA axis effects of multiple dose treatment with the MF/F combination will be assessed after 42 days of treatment in comparison to placebo and an active comparator in Study 2105, and after 9 doses in Study 2102. In addition, HPA axis assessments to be agreed upon with the Agency at a later date will be performed during the Phase III studies. The sponsors propose that these assessments will be adequate to assess the HPA axis safety of the combination formulations. Does the Agency agree?

Comment: We agree.

10/26/04 PIND 70,283 14

Slide 15

Comments regarding protocols

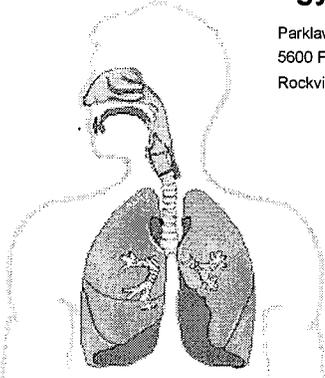
- Study 2102: Include comparisons for formoterol AUC_{0-12} and C_{max} and C_{min} for mometasone (in addition to the proposed parameters).
- Study 2104: Collect blood samples at 24 and 36 hr post dose (in addition to the proposed times) for mometasone and urine samples up to 24 hrs for formoterol (Ae_{0-24})
- Equivalence claims for PK parameters: Equivalence should not be claimed unless the 90% CIs are within 0.8-1.25.

10/26/04 PIND 70,283 15

Schering/Novartis stated that they accept the above comments. They noted, with regard to the third comment on Slide 15, that they had not intended to claim true equivalence, but rather they had meant comparability.

Slide 16

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10/26/04 PIND 70,283 16

Lori Garcia, Regulatory Project Manager

Drafted: LAG/November 23, 2004

Initialed: TPurohit-Sheth/November 29, 2004
LGilbert-McClain/November 29, 2004
RLostritto/November 29, 2004
EFadiran/November 23, 2004
BChowdhury/November 30, 2004

Finalized: LAG/Novmeber 30, 2004

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

/s/

Lori Garcia
11/30/04 11:39:44 AM