DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-518 **NDA APPROVAL**

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

Attention: Michael Belman
Director & Liasion, 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 (FDCA) for Dulera (mometasone furoate and formoterol fumarate) Inhalation Aerosol 100/5 and 200/5 micrograms.

We acknowledge receipt of your submissions dated June 4 and 16, July 1, 16 and 24, August 12 and 26, September 4 and 22, October 29 and November 4, 10, 13 and 25, 2009, January 11, 14, 22 and 29, February 3, 12 and 16, March 5 and 16, May 21 and 26 and June 10, 11, 15, 18, 21 and 22, 2010.

This new drug application provides for the use of Dulera (mometasone furoate and formoterol fumarate) Inhalation Aerosol for the treatment of asthma, in adults and children 12 years of age and older.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert, submitted June 22, 2010 and Medication Guide, submitted June 22, 2010. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on June 18, 2010, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)". Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22-518**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Your application for Dulera (mometasone furoate and formoterol fumarate) Inhalation Aerosol was not referred to an FDA advisory committee. The use of an inhaled corticosteroid and long-acting beta agonist (LABA) in combination are well established for the treatment of asthma and Dulera (mometasone furoate and formoterol fumarate) Inhalation Aerosol combines two active ingredients that are individually well studied in other formulations and devices in patients with asthma. Therefore, this application did not warrant discussion at an advisory committee meeting.

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 are waiving the pediatric study requirement for ages 0 to 4 years because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group **and** is not likely to be used in a substantial number of pediatric patients in this group. The role of LABAs in asthma therapy for patients 4 years of age and younger is not established.

We are deferring submission of your pediatric studies for ages 5 to 11 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed. In addition, you are attempting to develop an additional low strength formulation with an assessment for patients 5 to 11 years of age.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of the postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. The required studies are listed below.

1658-1 Deferred pediatric trial under PREA to compare the pharmacodynamics of DULERA with and without a spacer in children 5 to 11 years of age

Protocol Submission:	October 2010
Study Completion:	February 2012
Final Report Submission:	July 2012

1658-2 Deferred pediatric trial under PREA to compare the pharmacokinetics of DULERA with and without a spacer in children 5 to 11 years of age

Protocol Submission:	July 2012
Study Completion:	June 2014
Final Report Submission:	November 2014

1658-3 Deferred pediatric trial under PREA to evaluate the effects of DULERA on the HPA axis 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.

Protocol Submission:	May 2012
Study Completion:	October 2013
Final Report Submission:	March 2014

1658-4 Deferred pediatric trial under PREA to evaluate the safety and efficacy of multiple doses of mometasone MDI in children 5 to 11 years of age with asthma.

Protocol Submission:	April 2012
Study Completion:	March 2014
Final Report Submission:	August 2014

1658-5 Deferred pediatric trial under PREA to evaluate the safety and efficacy of DULERA compared to mometasone MDI in children 5 to 11 years of age with asthma. This study will be 12- 26 weeks duration.

Protocol Submission:	May 2014
Study Completion:	August 2016
Final Report Submission:	January 2017

1658-6 Deferred pediatric trial under PREA to evaluate the long-term safety of DULERA in children 5 to 11 years of age with asthma. This study will be 26 weeks duration with a 6 month extension

Protocol Submission:	July 2014
Study Completion:	October 2016
Final Report Submission:	March 2017

Submit final study reports to this NDA. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated "**Required Pediatric Assessment(s)**".

We note that you have fulfilled the pediatric study requirement for ages 12 to 17 years for this application.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to evaluate the risk of serious asthma outcomes (asthma related death, intubations, and hospitalizations) with the use of a long-acting beta agonist (LABA), included Dulera (mometasone and formoterol fumarate).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess serious asthma outcomes (asthma related death, intubations, and hospitalizations) with the use of a LABA.

Therefore, based on appropriate scientific data, FDA has determined that you are required, to conduct one or more postmarketing clinical trials with Dulera (mometasone furoate and formoterol fumarate) Inhalation Aerosol compared to inhaled corticosteroids in adults and adolescent patients with asthma, to evaluate the risk of serious asthma outcomes. Submit a proposal to address this requirement.

Submit the proposal to your IND, with a cross-reference letter to this NDA 22-518. Submit all final report(s) to your NDA 22-518. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Post-approval Agreements

We remind you of our agreements from your submissions dated November 25, 2009, January 14, 2010, and March 5, 2010, listed below:

1. (b) (4) will be utilized as the different laboratory (other than that of the manufacturer) to periodically verify the information on the supplier's certificate of analysis for HFA 227.

2. Re-evaluate the oleic acid individual fatty acid specifications within a period of two years after approval of the NDA, based on additional data.

3. Introduce methodology identical or equivalent/better than that contained within USP-NF General Chapter <401> for control of fatty acid composition in oleic acid.

4. Re -evaluate the drug product specifications for (b) (4) and the drug product specifications for degradation products "using the data from all available commercial stability batches once there are a minimum of 3 stability batches for each drug product strength where at least one batch has data through 24 months, the second batch has at least 12 months of stability data, and a third batch has at least 6 months of stability data.

5. Maintain specifications (i.e., a list of tests, the acceptance criteria and the test methods) in NDA 22-518 for each of the two drug substances.

6. Investigate the changes in particle size distribution of the emitted plume over the use life of the drug product and report the progress and submit results to the Agency within 6 months of the date of the information request, dated February 19, 2010.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). The details of the REMS requirements were outlined in our REMS notification letter dated February 18, 2010.

Your proposed REMS, submitted on June 22, 2010, and appended to this letter, is approved. The REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include but is not limited to the following:

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. An analysis of prescribers' understanding of the increased risk of asthma-related deaths and the safe use of LABAs.

iii. 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.

iv. A narrative summary with analysis of all reported asthma-related deaths during the reporting period.

v. Drug use patterns (reasons for use, patient demographics, length of therapy, prescribing medical specialties)

vi. 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 DCHP 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 to which you communicated
6. The information that the professional societies disseminated to its members and the timing for the dissemination

vii. 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.

Assessments of an approved REMS must also include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of FDCA.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 22-518
REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 22-518
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR NDA 22-518
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Eunice 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, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

Content of Labeling
Carton and Container Labeling
REMS

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/

BADRUL A CHOWDHURY
06/22/2010