# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**022518Orig1s000**

# SUMMARY REVIEW

**SUMMARY REVIEW OF REGULATORY ACTION**

| | |
|---|---|
| Date: | June 22, 2010 |
| From: | Badrul A. Chowdhury, MD, PhD<br>Director, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA |
| Subject: | Division Director Summary Review |
| NDA Number: | 22-518 |
| Applicant Name: | Schering Corporation |
| Date of Submission: | May 21, 2009 |
| PDUFA Goal Date: | June 22, 2010 |
| Proprietary Name: | Dulera |
| Established Name: | Mometasone furoate and formoterol fumarate |
| Dosage form: | Inhalation Aerosol |
| Strength: | (b) (4)<br>Mometasone furoate 100 mcg and formoterol fumarate 5 mcg, and<br>Mometasone furoate 200 mcg and formoterol fumarate 5 mcg |
| Proposed Indications: | Asthma |
| Action: | Approval for (b) (4) two dosage strengths (b) (4) |

## 1. Introduction

Schering Corporation submitted this 505(b)(1) application for use of Dulera (mometasone furoate and formoterol fumarate) Inhalation Aerosol (b) (4) 100/5 mcg, and 200/5 mcg for (b) (4) treatment of asthma (b) (4) in patients 12 years of age and older. The proposed doses are two inhalations twice-daily of Dulera (b) (4) 100/5 mcg, or 200/5 depending on asthma severity. The application is based on clinical efficacy and safety studies. This summary review will provide an overview of the application, with a focus on the clinical efficacy and safety studies. (b) (4)

The original PDUFA date for this application was March 22, 2010. On February 16, 2010, the Applicant submitted a response to clinical issues in the 74 day letter, which included a new clinical study report to provide additional support for (b) (4) dose strengths of Dulera. Because of the newly submitted clinical data, this submission was considered a major amendment and the PDUFA clock was extended to June 22, 2010.

## 2. Background

There are several drug classes available for use in patients with persistent asthma. These include inhaled corticosteroids (ICSs), inhaled long-acting beta-adrenergic agents (LABAs), leukotriene modifying drugs, methylxanthines, and omalizumab. ICSs are considered to be the most effective long-term therapy for persistent asthma, and are

commonly used as the first drug when a maintenance therapy is necessary. When an adequate dose of ICS has not provided adequate control, a second drug, such as a LABA is often added, preferably for a limited time period with the intent of discontinuation once asthma control is achieved and maintained. Since some patients with persistent asthma use both an ICS and a LABA, these two drugs have been put together in the same formulation and in the same device and marketed as inhaled combination products of convenience. There are three such combination products in the market in the United States. These are Advair Diskus and Advair HFA Inhalation Aerosol (both are a combination of fluticasone propionate and salmeterol xinafoate) and Symbicort (a combination of budesonide and formoterol fumarate). Advair and Symbicort contain different dose levels of inhaled corticosteroids and a single dose level of LABA. The Dulera combination product contains mometasone furoate and formoterol fumarate in a HFA propelled inhalation aerosol. Single component mometasone furoate and formoterol fumarate are approved and marketed in the United States as dry powder inhalers.

## 3. Chemistry, Manufacturing, and Controls

The proposed commercial drug product Dulera (mometasone furoate and formoterol fumarate) Inhalation Aerosol (b) (4) 100/5 mcg, and 200/5 mcg contains a suspension formulation of mometasone furoate and formoterol fumarate containing HFA 227 as the propellant, ethanol as a (b) (4) co-solvent, and oleic acid as a surfactant. The device contains a standard valve and canister with a standard press-and-breathe actuator with an integrated dose counter. There are (b) (4) proposed strengths – (b) (4) 100/5 mcg, and 200/5 mcg. The ex-mouthpiece delivered doses of the (b) (4) strengths are (b) (4) 100 mcg, and 200 mcg mometasone furoate, and 5 mcg formoterol fumarate, respectively. Each Dulera canister is intended to deliver 120 actuations.

Mometasone furoate is manufactured by Schering Corporation in Singapore, and formoterol fumarate is manufactured by Astellas Pharma chemicals Co., in Japan. The drug product is manufactured by 3M Health Care Ltd in England. All manufacturing and testing facilities associated with this application have acceptable inspection status. The various DMFs associated with the manufacture of the product are adequate.
A 24 month expiry is proposed for Dulera, which is supported by stability data.

There were several CMC issues that were resolved during review of the application. One notable point was that the formoterol monotherapy product used in clinical trials was different than Dulera. It used a different propellant - HFA 134a, had lactose as an excipient, and used a different valve. Comparability between the formoterol monocomponent used in clinical trials and Dulera was established by assessment of various in vitro drug delivery characteristics.

## 4. Nonclinical Pharmacology and Toxicology

The Applicant submitted a bridging toxicology program that included general toxicology studies of 13 weeks duration in rats and dogs. Since the toxicity profiles of mometasone

furoate and formoterol fumarate by systemic route and inhalation route are well known, this limited bridging program is adequate. In the toxicology studies submitted, there was no evidence of toxicological interactions between mometasone furoate and formoterol fumarate.

## 5. Clinical Pharmacology and Biopharmaceutics

The Applicant submitted a limited clinical pharmacology program that evaluated the pharmacokinetic profile of Dulera. Since the pharmacokinetic profiles of mometasone furoate and formoterol fumarate by inhalation route are well known, the limited program is adequate. The applicant did not conduct a relative bioavailability study in patients with asthma, but a study in healthy volunteers showed that systemic exposure of mometasone furoate from Dulera was lower compared to Asmanex Twisthaler at the same nominal dose (AUC was approximately 52% and 25% lower on day 1 and day 5, respectively). Studies using oral dosing of labeled and unlabeled mometasone have demonstrated that systemic bioavailability of mometasone is negligible (less than 1%). The lower exposure for mometasone from Dulera compared to Asmanex Twisthaler assures systemic safety, such as HPA axis effect, for the mometasone component in Dulera, but may result in lower delivery to the lung and therefore lower efficacy for the mometasone component in Dulera. The Applicant has adequately assessed the HPA axis effect of Dulera in separate studies (discussed in section 8).

## 6. Clinical Microbiology

Not applicable.

## 7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Some characteristics of the relevant clinical studies that form the basis of the review and regulatory decision for this application are shown in Table 1. The general expectation of developing a combination product containing an ICS and a LABA are briefly described below, followed by discussion of the design and conduct of some of these studies and the efficacy findings and conclusions. Safety findings are discussed in the following section.

**Table 1. Relevant clinical studies**

| **ID** Year * | **Study type** | **Study duration** | **Patient Age, yr** | **Treatment groups#** | **N (ITT)** | **Primary efficacy variables** | **Countries** |
|---|---|---|---|---|---|---|---|
| **Single ingredient dose selection and pivotal studies** | | | | | | | |
| **208** 1998 | Dose ranging | 12 week | 12 - 81 | Mom 25 mcg, 2 puff BID<br>Mom 100 mcg, 2 puff BID<br>Mom 200 mcg, 2 puff BID<br>Mom 300 mcg, 2 puff BID<br>Van 168 mcg BID<br>Placebo | 71<br>73<br>74<br>73<br>72<br>72 | 1-4 hr pose dose FEV1 | US |
| **225** 1998 | Efficacy and Safety | 12 week | 12 - 72 | Mom 25 mcg, 2 puff BID<br>Mom 100 mcg, 2 puff BID<br>Van 168 mcg BID | 58<br>57<br>58 | 1-4 hr post dose FEV1 | US |

| **ID** Year * | **Study type** | **Study duration** | **Patient Age, yr** | **Treatment groups#** | **N (ITT)** | **Primary efficacy variables** | **Countries** |
|---|---|---|---|---|---|---|---|
| | | | | Placebo | 59 | | |
| **200** 1998 | Efficacy and Safety | 12 week | 12 - 76 | Mom 50 mcg, 2 puff BID<br>Mom 100 mcg, 2 puff BID<br>Mom 200, 2 puff BID<br>Flovent 125 mcg BID | 176<br>182<br>176<br>176 | 1-4 hr post dose FEV1 | EU, South America, South Africa |
| **224** 1999 | Efficacy and Safety | 12 week + 9 mo OLE | 12 - 83 | Mom 200 mcg, 2 puff BID<br>Mom 400 mcg, 2 puff BID<br>Placebo | 42<br>43<br>38 | Oral steroid requirement | US |
| **6144** 2002 | Dose ranging | Single dose | 18-67 | For 5 mcg<br>For 10 mcg<br>For 20 mcg<br>FA 12 mcg<br>FA 24 mcg<br>Placebo | 26 | FEV1 | Netherlands |
| **Combination product dose selection, pivotal, and supportive studies** | | | | | | | |
| **4073** 2008 | Efficacy and Safety | 26 week | 12-79 | Dul 50/5 mcg, 2 puff BID<br>Mom 50 mcg, 2 puff BID<br>For 5 mcg, 2 puff BID<br>Placebo | 155<br>156<br>146<br>129 | Post dose FEV1 + Exacerbation | US, Canada, EU, Asia, S America |
| **4334** 2008 | Efficacy and Safety | 26 week | 12-76 | Dul 100/5 mcg, 2 puff BID<br>Mom 100 mcg, 2 puff BID<br>For 5 mcg, 2 puff BID<br>Placebo | 166<br>169<br>135<br>128 | Post dose FEV1 + Exacerbation | US, Canada, EU, Asia, S America, Russia |
| **4431** 2008 | Efficacy and Safety | 26 week | 12-84 | Dul 100/5 mcg, 2 puff BID<br>Dul 200/5 mcg, 2 puff BID<br>Mom 200 mcg, 2 puff BID | 230<br>251<br>237 | Post dose FEV1 | US, Europe, S America |
| **4139** 2008 | Safety | 52 week | 12-75 | Dul 100/5 mcg, 2 puff BID<br>Dul 200/5 mcg, 2 puff BID<br>Advair 250/50, 2 puff BID<br>Advair 500/50, 2 puff BID | 141<br>130<br>68<br>65 | None | S America |
| **3705** 2008 | HPA axis | 6 week | 18-64 | Dul 100/5 mcg, 2 puff BID<br>Dul 200/5 mcg, 2 puff BID<br>Advair 250/50, 2 puff BID<br>Placebo | 15<br>17<br>16<br>18 | None | US |
| **4703** 2008 | Dose counter | 4 week | 12-82 | Dul 100/5 mcg, 2 puff BID | 261 | None | US |
| **4705** 2008 | Efficacy and Safety | 12 week | 12-82 | Dul 200/5 mcg, 2 puff BID<br>Advair HFA 230/21, 2 puff BID | 371<br>351 | Post dose FEV1 | US, Canada, Europe, S America |
| **5122** 2009 | Dose ranging | 2 week | 18-73 | Dul 50/5 mcg, 2 puff BID<br>Dul 100/5, 2 puff BID<br>Dul 200,5, 2 puff BID<br>Asmanex 100 mcg, 2 puff BID<br>Mom 100 mcg, 2 puff BID<br>Placebo | 20<br>17<br>12<br>15<br><br>16<br>13 | eNO | US, EU |

*Year study subject enrollment ended
# Mom = mometasone furoate in same formulation and device as in Dulera; Van = Vanceril (beclomethasone dipropionate) Inhalation Aerosol; Flovent (fluticasone furoate) Inhalation Aerosol CFC propelled; For = formoterol fumarate in comparable formulation and device as in Dulera (see section 3 for differences); FA = Foradil Aerolizer; Dul = mometasone furoate and formoterol fumarate;
Note: All doses are ex-mouthpiece (end of the actuator from where the patient inhales)

From an efficacy standpoint, combination products containing an ICS and a LABA should contain doses of individual components for which efficacy have been established, and the clinical program specific to the combination product should demonstrate the

contribution of each component present in the combination product by replicate studies. The submitted clinical program satisfies these expectations as discussed below.

Justification of dose selection and efficacy of the two active ingredients:

The Applicant has provided adequate justification and data to support the selection of doses of the two active ingredients. The main support for the formoterol fumarate dose comes from study 6144 where three doses of formoterol fumarate in formulation and device comparable to Dulera were compared to two doses of Foradil Aerolizer in patients with asthma (Table 1). The FEV1 time-profile curve showed numerical dose-response for both the products, which is necessary for comparing products (Figure 1). In this study efficacy for the 5 mcg formoterol strength (in Dulera) was lower than others, and the two higher strengths of the two products performed similarly (Figure 1). This study is adequate to support carrying forward the 10 mcg formoterol dose to further studies of Dulera. The support for mometasone furoate comes from studies 208, 225, 200, and 224 (Table 1). In these studies all doses of mometasone furoate were effective as measured by FEV1 and other efficacy variables. Post dose FEV1 change from baseline for mometasone over placebo ranged from approximately 250 mL to 350 mL. Although trough FEV1 is typically necessary to assess ICS effect, the overall data are supportive of efficacy of multiple doses of mometasone furoate. The application carried forward the (b) (4) (b) (4), 100 mcg, and 200 mcg strengths to further studies for Dulera. There was replicate evidence of efficacy for the mometasone 100 mcg and 200 mcg strengths. (b) (4) (b) (4) Dosing frequency assessments for formoterol and mometasone were not done. This is acceptable because dosing frequency has been previously assessed for both these drug substances for asthma in other formulations.

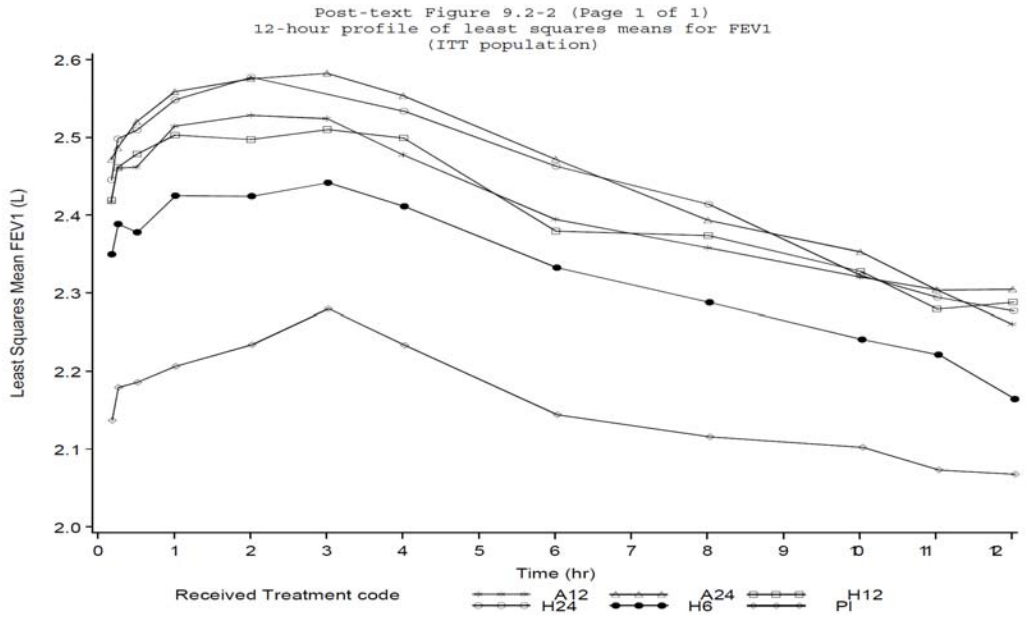


**Figure 1. Study 6144, LS mean FEV1 time profile over 12 hours**

b. Design and conduct of the studies

Studies 4073, 4334, and 4431 are discussed in this section because these are the pivotal studies submitted to demonstrate contribution of each component present in Dulera. Studies 4073 and 4334 also allow independent efficacy assessment of mometasone furoate and formoterol fumarate compared to placebo.

Studies 4073, 4334, and 4431, were similar in design and conduct. All were randomized, double-blind, parallel group in design, and conducted in patients with mild-to-moderate asthma with percent predicted FEV1 60-85% (lower bound was 50% in study 4431) of normal. Study 4334 required patients to be at certain doses of ICS to enroll more severe patients in this study compared to study 4073. Study 4431 also required patients to be at certain doses of ICS, which were generally higher than those allowed for study 4334 with the intent of enrolling more severe patients in this study compared to study 4334. Studies 4073 and 4334 had a 2-3-week run-in period followed by 26-week randomized treatment period; study 4431 had a 12-week randomized treatment period. Studies 4073 and 4334 had two primary efficacy variables: change in FEV1 AUC 0-12 hours from baseline to week 12 (to show the contribution of the formoterol fumarate component of the combination), and time to first severe asthma exacerbation (to show the contribution of the mometasone furoate component of the combination). Time to first severe asthma exacerbation was defined as the occurrence of any of the following: decrease in absolute FEV1 below the treatment period stability limit (80% of the average of the two predose FEV1 measurements taken 30 minutes and immediately prior to the first dose of randomized study medication); decrease in AM or PM PEFR below the treatment period of stability limit (70% of the respective AM or PM PEFR obtained over the last 7 days of the run-in period); emergency treatment; hospitalization; treatment with additional excluded asthma medication (e.g., OCS). Study 4431 had one primary efficacy variable: change in FEV1 AUC 0-12 hours from baseline to week 12. Asthma exacerbation was assessed as a secondary variable in 4431. Other pertinent efficacy variables assessed in these studies were trough FEV1 (an important measure to show contribution of corticosteroid), AQLQ, ACQ, PEFR, symptom scores, and nocturnal awakenings. Safety assessments included recording of adverse events, vital signs, physical examination, clinical laboratory evaluation, and 12-lead ECG.

c. Efficacy findings and conclusions

The submitted clinical program supports efficacy of Dulera 100/5 mcg and Dulera 200/5 mcg for the treatment of asthma in patients 12 years of age and older. (b) (4)

Results of the three studies that tested three dose strengths of Dulera against its active ingredients and placebo were generally statistically significant for relevant endpoints that show contribution of each component, except for trough FEV1 for (b) (4) which calls into question the contribution of (b) (4)

(b) (4) in Dulera (b) (4)(Table 2). Furthermore, as discussed above under the subheading "Justification of dose selection of the two active ingredients," there was replicate evidence of efficacy for the mometasone 100 mcg and 200 mcg strengths, (b) (4) There was numerical benefit of Dulera 200/5 mcg over Dulera 100/5 mcg supporting approval of both these strengths.

The effect size for mean trough FEV1 improvement for mometasone furoate (b) (4) component of Dulera over placebo at week 12 was approximately 0.12 L (Table 2), which were approximately about half the effect sizes for mean trough FEV1 improvement for Asmanex Twisthaler (mometasone furoate inhalation powder) over placebo at week 12 for similar ex-mouthpiece doses (trough FEV1 numbers from Asmanex product label).

**Table 2. Results of primary efficacy variables and trough FEV1 from the pivotal efficacy studies**

| | **FEV1 AUC 0-12 hr** LS Mean change from baseline to Week 12 (L | **FEV1 Trough** LS Mean change from baseline at Week 12 (L) | **Time to Asthma Exacerbation** |
|---|---|---|---|
| (b) (4) | | | |
| **Study 4334** | | | |
| Dul 100/5 vs Mom 100 | 1.81 (p<0.001) | | |
| Dul 100/5 vs For 5 | | 0.13 (p<0.001) | p<0.001 |
| Dul 100/5 vs placebo | 2.54 (p<0.001) | 0.18 (p<0.001) | p<0.001 |
| Mom 100 vs placebo | | 0.12 (p<0.001) | |
| For 5 vs placebo | 1.36 (p=0.009) | | |
| **Study 4431** | | | |
| Dul 200/5 vs Mom 200 | 2.15 (p<0.001) | 0.09 (p=0.006) | |
| Dul 200/5 vs Dul 100/5 | 0.60 (p=0.096) | 0.05 (p=0.145) | |

# Dul = mometasone furoate and formoterol fumarate; Mom = mometasone furoate in same formulation and device as in Dulera; For = formoterol fumarate in comparable formulation and device as in Dulera (see section 3 for differences);
Note: All doses are ex-mouthpiece (end of the actuator from where the patient inhales)

**Table 3a. Number and percentage of patients meeting the predefined criteria of measures of deteriorations of asthma (used in the protocol to define "severe asthma exacerbation")**

| | Study 4073 (b) (4) | Study 4334 | | | |
|---|---|---|---|---|---|
| | | Dul 100/5 N=191 | Mom 100 N=192 | For 5 N=202 | Pbo N=196 |
| Overall clinical deteriorations or reductions in lung function | | 58 (30.4) | 65 (33.9) | 109 (54.0) | 109 (55.6) |
| Decrease in FEV1 * | | 18 (9.4) | 19 (9.9) | 31 (15.3) | 41 (20.9) |
| Decrease in PEFR ** | | 37 (19.4) | 41 (21.4) | 62 (30.7) | 61 (31.1) |
| Emergency treatment | | 0 | 1 (0.5) | 4 (2.0) | 1 (0.5) |
| Hospitalization | | 1 (0.5) | 0 | 0 | 0 |
| Use of excluded medications† | | 2 (1.0) | 4 (2.1) | 17 (8.4)# | 8 (4.1) |

* FEV1 below the treatment period stability limit (80% of the average of the two predose FEV1 measurements taken 30 minutes and immediately prior to the first dose of randomized study medication)
**AM or PM PEFR below the treatment period of stability limit (70% of the respective AM or PM PEFR obtained over the last 7 days of the run-in period);
# 16 patients received systemic steroids; 1 patient received formoterol DPI
† Patients received systemic steroids except one patient in Study 4334 in the For 5 arm who received formoterol DPI

**Table 3b. Number and percentage of patients meeting the predefined criteria of measures of deteriorations of asthma (used in the protocol to define "severe asthma exacerbation") in Study 4431**

| | Study 4431 | | |
|---|---|---|---|
| | Dul 100/5 N=233 | Dul 200/ 5 N=255 | Mom 200 N=240 |
| Clinically judged deterioration in asthma or reduction in lung function* | 29 (12.4%) | 31 (12.2%) | 44 (18.3%) |
| Decrease in FEV1 * | 23 (9.9) | 17 (6.7) | 33 (13.8) |
| Decrease in PEFR ** | 2 (0.9) | 4 (1.6) | 3 (1.3) |
| Emergency treatment | 3 (1.3) | 1 (0.4) | 1 (0.4) |
| Hospitalization | 0 | 1 (0.4) | 0 |
| Use of excluded medications† | 5 (2.1) | 8 (3 1)# | 12 (5.0) |

* FEV1 below the treatment period stability limit (80% of the average of the two predose FEV1 measurements taken 30 minutes and immediately prior to the first dose of randomized study medication)
** AM or PM PEFR below the treatment period of stability limit (70% of the respective AM or PM PEFR obtained over the last 7 days of the run-in period);
# 7 patients received systemic steroids; 1 patient received Ventolin.
† Patients received systemic steroids except one patient in the Dulera 200/5 arm who received albuterol.

(b) (4)

(b) (4)

[redacted]

Various secondary efficacy variables were supportive of the primary and other endpoints discussed above. The results of the AQLQ were numerically supportive of Dulera, but the change from baseline to end of treatment corrected for change from placebo did not cross the MID of 0.5 (Table 4). For Dulera 100/5 the change over placebo was 0.50 (95% CI 0.32, 0.68). The improvement for AQLQ was less than other ICS plus LABA combination products. On similar matrix of measurement, for Advair Diskus 250/50 mcg the AQLQ change was 1.29, for Advair HFA Inhalation Aerosol 45/21 mcg was 1.14, and for Symbicort 160/4.5 mcg was 0.70.

**Table 4. LS mean AQLQ scores at baseline and change from baseline at week 26***

| | Study 4073 (b) (4) | Study 4334 | | | |
|---|---|---|---|---|---|
| | | Dul 100/5 | Mom 100 | For 5 | Pbo |
| Baseline | | 5.38 | 5.40 | 5.51 | 5.67 |
| Change at week 26 | | 0.49 | 0.37 | 0.05 | -0.01 |
| Change over placebo | | 0.50 | 0.38 | 0.05 | - |

Based on LOCF imputation*

## 8. Safety

a. Safety database

The safety assessment of Dulera for patients 12 years of age and older was primarily based on studies shown in Table 1. The total number of patients exposed to Dulera is reasonable to assess safety.

b. Safety findings and conclusion

The safety data do not raise safety concerns in the asthma patients that would preclude approval. There were three deaths, but none related to asthma. The deaths were due to unrelated events of electrocution, gastric cancer, and uterine cancer. Serious adverse events were few and did not suggest a new safety signal. There were serious adverse reactions of lens disorders and increases in intraocular pressure, which are known reactions to ICS. There were no asthma-related deaths, or asthma-related intubations. Common adverse events were typical for this class of drugs in asthma patients, such as oral candidiasis, nausea, headache, and pharyngolaryngeal pain.

HPA axis was assessed in a dedicated 6 week study and in the 52 week safety study (Table 1). There was a trend in the dose-dependent effect on plasma cortisol 24 hour AUC suggestive of a systemic effect of ICS. There was no HPA axis suppression.

The functionality of the integrated dose counter was satisfactorily assessed in a dedicated study (Table 1).

c. REMS/RiskMAP

Like other LABA containing products approved for asthma, Dulera will have a REMS limited to a Medication Guide and a Communication Plan.

## 9. Advisory Committee Meeting

An advisory committee was not convened for this application. ICS and LABA, used either alone or in combination are well studied in patients with asthma, and Dulera combines two active ingredients that are individually well studied in other formulations and devices in patients with asthma. The efficacy and safety findings in the clinical program were fairly obvious and did not warrant discussion at an advisory committee meeting.

## 10. Pediatric

The Applicant has proposed the asthma indication in patients 12 years of age and older and requested deferral of clinical studies in patients 5 to 11 years of age with asthma and a waiver in patients from 0 to 4 years of age with asthma. This proposal is acceptable. Deferral of studies in patients 5 to 11 years of age is reasonable because further evaluation of individual components and development of a lower strength product may be necessary for evaluation in patients 5 to 11 years of age. A waiver in children less than 5 years of age is reasonable as the use of a combination product containing ICS and LABA in patients younger than 4 to 5 years of age is generally not warranted. The request for deferral and waiver was discussed at the Center's Pediatric Review Committee (PeRC) meeting held on March 3, 2010. The PeRC was in agreement with the deferral and waiver request discussed above.

The Applicant has proposed the following studies to evaluate the efficacy and safety of mometasone furoate/formoterol in patients 5 to 11 years of age (Table 5).

**11. Other Relevant Regulatory Issues**

a. DSI Audits

A DSI audit was requested for 2 clinical study sites based on high enrollment. Final reports of the DSI inspections revealed adherence to Good Clinical Practices. Minor deficiencies were noted, but these were isolated and deemed unlikely to impact data integrity. During review of the submission no irregularities were found that would raise concerns regarding data integrity. No ethical issues were present. All studies were performed in accordance with acceptable ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. Three investigators had significant financial interest in the Applicant. The number of subjects that these investigators enrolled was not large enough to alter the outcome of any study. Furthermore, the multi-center nature of the studies makes it unlikely that these financial interests could have influenced or biased the results of these studies.

c. Others

There are no outstanding issues with consults received from DDMAC, DMEPA, or from other groups in CDER.

**12. Labeling**

a. Proprietary Name

There is no issue with the proposed proprietary name Dulera. The proposed proprietary name was accepted by DMEPA.

b. Physician Labeling

The Applicant submitted a label in the Physician's Labeling Rule format that contained information generally supported by the submitted data. Various changes to different sections of the label were made to reflect the data accurately and better communicate the findings to health care providers. (b) (4) The labeling contains a LABA safety related Boxed Warning for asthma-related death and (b) (4) The language and the Boxed Warning and other pertinent sections of the label are consistent with the changes that were made by the Agency for all LABA containing products on June 2, 2010. The label was reviewed by various disciplines of this Division, DRISK, DMEPA, and by DDMAC. The Division and Schering have agreed on the final labeling language.

c. Carton and Immediate Container Labels

The carton and immediate container labels were reviewed by various disciplines of this Division, ONDQA, and DMEPA, and found to be acceptable.

d. Patient Labeling and Medication Guide

A Medication Guide was required as discussed in section 8C above.

**13. Action and Risk Benefit Assessment**

a. Regulatory Action

The applicant has submitted adequate data to support approval of Dulera 100/5 mcg and Dulera 200/5 mcg at doses of two inhalations twice daily for the treatment of asthma in patients 12 years of age and older. The action on this application for these two dose strengths will be Approval.

(b) (4)

b. Risk Benefit Assessment

The overall risk benefit assessment supports approval of Dulera 100/5 mcg and Dulera 200/5 mcg. Dulera is a combination of an ICS (mometasone furoate) and a LABA (formoterol fumarate) for the treatment of asthma. ICS and LABA are established pharmacological classes for the treatment of asthma and both components of Dulera are currently available as orally inhaled products for use in patients with asthma. The major risks associated with use of the inhaled mometasone component present in Dulera are typical of ICSs and include infection, adrenal suppression, and glaucoma. The major risks associated with use of inhaled formoterol fumarate are the known risk of serious asthma outcomes (asthma related deaths, intubations, and hospitalizations). The benefits with use of inhaled mometasone furoate and inhaled formoterol fumarate are known benefits of these two drugs for asthma, such as improvement in airflow, nocturnal awakenings, and other symptoms. The submitted data show that the dose of formoterol fumarate proposed for Dulera is similar to the single ingredient formoterol fumarate product approved for use, and the dose of mometasone furoate proposed for Dulera is

similar (but with possible less systemic exposure and less efficacy) to the single ingredient mometasone furoate product approved for use. Marketing of this combination product is further justified by the submitted efficacy and safety data summarized in this review. There are three ICS and LABA combination products approved for marketing in the United States. These are combinations of fluticasone furoate and salmeterol xinafoate (Advair Diskus and Advair Inhalation Aerosol), and a combination of budesonide and formoterol (Symbicort Inhalation Aerosol). Dulera will provide patients with another choice of a combination product.

(b) (4)

There are two issues with Dulera 100/5 mcg and Dulera 200/5 mcg worth noting. These are the possibility of a lower efficacy benefit for the mometasone furoate component of Dulera compared to Asmanex Twisthaler at a similar ex-mouthpiece dose, and the lack of availability of the single ingredient mometasone furoate in a similar formulation and device as Dulera. These two issues are further discussed below.

The efficacy benefit of the mometasone component of Dulera may be less than that of Asmanex Twisthaler (mometasone furoate inhalation powder) at similar ex-mouthpiece doses. There are three pieces of data that supports this possibility. They are mentioned elsewhere in this document (Section 5 and Section 7) and summarized again here. First, in healthy volunteers systemic exposure of mometasone furoate from Dulera was lower compared to Asmanex Twisthaler at the same nominal dose (AUC was approximately 52% and 25% lower on day 1 and day 5, respectively). For mometasone furoate, which has systemic bioavailability of less than 1%, lower systemic exposure may reflect lower delivery to the lung and, therefore, lower efficacy. Second, the effect sizes for mean trough FEV1 improvement for the mometasone furoate component of Dulera over placebo at week 12 was approximately 0.12 L, which were about half or less than the effect sizes for mean trough FEV1 improvement for Asmanex Twisthaler (mometasone furoate inhalation powder) over placebo at week 12. Trough FEV1 is a well accepted surrogate measure of ICS efficacy. Third, improvement in AQLQ with Dulera seems to be less than that of Advair and Symbicort. The QOL instrument of AQLQ is a validated instrument for assessment of asthma. For Dulera 100/5 mcg, the change from baseline to end of treatment corrected for change from placebo for overall AQLQ was 0.50 (95% CI 0.32, 0.68). On similar matrix of measurement, for Advair Diskus 250/50 mcg the AQLQ change was 1.29, for Advair HFA Inhalation Aerosol 45/21 mcg was 1.14, and for Symbicort 160/4.5 mcg was 0.70. While Dulera AQLQ change did not cross the MID of 0.5, the other three products crossed the MID of 0.5. However, the last two pieces of data discussed above, trough FEV1 and AQLQ, carry the limitations of cross study comparisons. The rationale for allowing marketing of a drug product with possible less comparative benefit than other marketed products is to provide patients with choice.

The lower systemic exposure with Dulera compared to Asmanex Twisthaler (discussed above) will make it somewhat difficult for patients to switch between Dulera and Asmanex Twisthaler and maintain consistent exposure to mometasone furoate. This is

unlikely to lead to serious safety issues because the exposure, and potentially efficacy, with Asmanex Twisthaler is likely higher for the ICS component compared to Dulera at the same ex-mouthpiece dose. Also, the presence of mometasone furoate as a fixed dose combination product in Dulera changes the pattern of its use compared to Asmanex Twisthaler where the lower efficacy for the mometasone furoate component may have less of a consequence as patients are stepped down from the combination product Dulera to the single ingredient product Asmanex Twisthaler. Currently, there is no single ingredient mometasone furoate in a similar formulation and device as Dulera available on the market. The situation is the same as for Symbicort. For both these products, patients on a stepped care approach to the management of asthma may need to switch device and drug product if they wish to stay with the same ICS when a LABA is added or removed. (b) (4) . Ideally, the marketing of the mometasone furoate monocomponent would have preceded or coincided with the marketing of Dulera, but the regulatory precedent of Symbicort with no reported safety issues does not justify changing standards.

c. Post-marketing Risk Management Activities

A Risk Evaluation and Mitigation Strategy (REMS) will be required to manage the risk of serious asthma outcomes with LABA and help ensure the safe use of Dulera. The REMS includes a Medication Guide and Communication Plan, which is consistent with the REMS for other LABA products. The Communication Plan includes a Dear Healthcare Provider letter and educational materials for professional societies.

d. Post-marketing Study Commitments

The major post-marketing requirements (PMR) will be to address the safety of Dulera on serious asthma outcomes (asthma deaths, intubations, and exacerbations). All Applicants of approved LABA products for asthma are required to conduct a post-marketing large safety trial to assess the risk of serious asthma outcomes. Because Dulera contains formoterol furoate, which is currently approved for marketing, the safety study will be conducted as a PMR. Additional requirements included pediatric trials in patients 5 years and older as discussed in Section 10. The following are post-marketing requirements:

- Conduct one or more postmarketing clinical trials with DULERA 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).
- 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
- 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
- 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
- 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
- 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 to 26 weeks in duration.
    - Protocol Submission: May 2014
    - Study Completion: August 2016
    - Final Report Submission: January 2017
- 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

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

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/s/

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BADRUL A CHOWDHURY
06/22/2010