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APPLICATION NUMBER:

205636Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	February 11, 2015
From	Nikolay P. Nikolov, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 205,636
Supplement#	0
Applicant	Teva Pharmaceuticals
Date of Submission	Received May 05, 2014
PDUFA Goal Date	March 04, 2015
Proprietary Name / Established (USAN) names	ProAir RespiClick / Albuterol Sulfate, multi-dose dry powder inhaler, MDPI
Dosage forms / Strength	Multi-Dose Dry Powder Inhaler, MDPI / 97 mcg (base) provided as 117 mcg of the albuterol sulfate salt (emitted dose 90 mcg) per actuation
Proposed Indications	<ul style="list-style-type: none">• Treatment or prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease• Prevention of exercise-induced bronchospasm in patients 12 years of age and older
Recommended:	<i>Approval, with revisions to proposed labeling</i>

1. Introduction

This memorandum reviews the regulatory background and the evidence supporting the efficacy and safety of this 505(b)(2) new drug application (NDA) for albuterol sulfate inhalation powder, for the treatment or prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease and prevention of exercise-induced bronchospasm in patients 12 years of age and older submitted by Teva.

Albuterol sulfate, the active component, is a sympathomimetic amine with selective beta-2 adrenergic agonist properties. When administered by inhalation or by the oral route, the primary effect is on the bronchial smooth muscle in the lungs acting as a bronchodilator. Albuterol sulfate is short-acting β_2 -agonist (SABA) bronchodilator with significant effect by 15 minutes and demonstrable effects for 3 to 4 hours. SABAs are the mainstay in the management of asthma, and inhaled albuterol has been established as the most widely used treatment for acute relief of bronchospasm and exercise-induced bronchospasm.

The currently available presentations containing albuterol sulfate in the United States are “press-and-breathe” metered-dose inhalers (MDIs) which require coordination of actuation with inspiration. To minimize the need for such coordination, Teva has developed an albuterol multidose dry-powder inhaler (Albuterol MDPI), the subject of this NDA, which is a breath-actuated presentation and a new dosage form for albuterol. If approved, Albuterol MDPI, will be the first dry-powder inhaler albuterol available on the US market.

2. Background

Asthma is a common chronic disease worldwide and one of the most common chronic disease in childhood. In the United States, asthma affects more than 22 million persons, including 6 million children. It is a complex disorder characterized by variable and recurring symptoms such as wheezing, shortness of breath, chest tightness, and cough, intermittent partially or completely reversible airflow obstruction, bronchial hyperresponsiveness as measured by lung function testing, and an underlying inflammation potentially resulting in airway remodeling. Airway hyperresponsiveness or bronchial hyperreactivity, the hallmark of the disease, is an exaggerated response to numerous exogenous and endogenous stimuli. The degree of airway hyperresponsiveness generally correlates with the clinical severity of asthma. The diagnosis of asthma includes a determination of symptoms of recurrent episodes of airflow obstruction or airway hyperresponsiveness, reversible airflow obstruction, and exclusion of alternative diagnoses. The goal of asthma therapy is asthma control achieved by proper assessment and monitoring, education, control of environmental factors and co-morbid conditions that affect asthma, and medications as set forth by the Expert Panel Report 3.¹ The medications for management of asthma are categorized into (1) long-term control medications to achieve and maintain control of persistent asthma, and (2) quick-relief medications. Category 1 therapies include inhaled corticosteroids, LABA, methylxanthines, such as theophylline, leukotriene modifiers, and immunomodulators, such as anti-IgE antibody. Quick symptom relief therapies include, SABAs, such as albuterol, and systemic corticosteroids. The type, amount, and scheduling of medications is individual and is determined by a stepwise approach based on the individual's level of asthma severity and control. Other considerations include patient's age, pregnancy, surgery, and co-morbid conditions.

Exercise-induced bronchospasm (EIB) is the term commonly used to describe the transient increase in airway resistance that follows vigorous exercise.² The prevalence of EIB ranges from 5% to 20% in the general population, to even 100% in people with uncontrolled asthma. The diagnosis of EIB is usually made by exercise testing. An individual's response to exercise is generally expressed by the maximal percent fall in forced expiratory volume in one second (FEV₁). The maximal percent fall is considered an expression of severity of EIB and is calculated by subtracting the lowest FEV₁ value from the pre-exercise value and expressing it as a percentage of the pre-exercise value. Both European Respiratory Society (ERS) and American Respiratory Society (ATS) recommendations set a fall threshold of 10% as a diagnostic criterion for EIB and a value greater than 30% as a marker of severe bronchial hyperreactivity. The FDA Guidance for Industry: *Exercise-Induced Bronchospasm (EIB) – Development of Drugs to Prevent EIB*³ recommends an FEV₁ fall threshold of 20% as a diagnostic criterion for EIB. The main principle of treating EIB involves reversing the bronchial obstruction induced by exercise with bronchodilators or preventing it with daily use of either controller drugs in people with asthma, or drugs that inhibit symptoms and improve pulmonary function immediately before exercise. Pretreatment before exercise includes mast

¹ Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma - Summary Report 2007: <http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines>

² Weiler JM, et al., Pathogenesis, prevalence, diagnosis, and management of exercise-induced bronchoconstriction: a practice parameter, *Ann Allergy Asthma Immunol.* 2010 Dec;105(6 Suppl):S1-47

³ <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071648.pdf>

cell stabilizers, leukotriene antagonists, SABA, and long-acting beta2- agonists (LABA).⁴ The mechanisms of protection by SABA and LABA are believed to be related to (1) beta2-receptor induced relaxation of bronchial smooth muscle, which opposes the effects of the various mediators of bronchoconstriction, and (2) beta2 receptor-induced inhibition of mediator release from mast cells. When administered in a single dose, SABA and LABA are effective and safe in preventing the symptoms of EIB. However, longer-term administration of inhaled beta2-agonists induces tachyphylaxis, a partial drug tolerance, within days to weeks from the start of treatment, and use in this manner is discouraged. The clinical development of Albuterol MDPI for the prevention of EIB claim followed the principles outlined in the 2002 FDA Guidance for Industry: *Exercise-Induced Bronchospasm (EIB) – Development of Drugs to Prevent EIB*.⁵

Of note, while multiple single-ingredient albuterol sulfate inhalation aerosols have been approved in the US, there are no inhalation dry powder albuterol products. To evaluate the potential impact on safety and efficacy of the new dosage form, i.e. albuterol dry powder inhaler, Teva conducted a stand-alone clinical development program in the US in support of this NDA. The clinical development program supporting the current Application followed the recommendations provided by the Division during the multiple pre-submission interactions. Specifically, at the pre-IND meeting in March 2009, the Division advised the applicant that because the proposed Albuterol MDPI is a novel formulation in a novel device, evaluation of efficacy and safety would entail a full clinical development program of a new drug-device combination product, including a dose-ranging study comparing efficacy and safety to a comparator product, a cumulative dose pharmacodynamic efficacy and safety study in patients with asthma and acute bronchospasm, and replicate 12-week randomized, placebo controlled chronic dosing efficacy and safety studies in patients with asthma. At an end-of-phase 2 meeting in August 2010, the Division advised the applicant that the phase 3 program should include a representative proportion of 12 to 16 year-old patients and should be conducted in diverse geographic regions with high humidity as well as low humidity to assess the potential of caking of the product with high ambient humidity.

The data in this submission were derived from eight clinical studies as summarized in Table 1: a cumulative dose Phase 1 study, a 5-way single-dose Phase 2 dose-ranging study and 5 Phase 3 studies that included 3 pivotal efficacy studies. Of note, three versions of the Albuterol MDPI device were used in the clinical studies; importantly, the to-be-marketed device, N8, was used in the confirmatory Phase 3 studies. Detailed description of the design, conduct, efficacy and safety of the individual studies are provided in Section 7 and Section 8 below. The data provided in the submission were deemed adequate to evaluate the efficacy and safety of Albuterol MDPI for the proposed indications.

⁴ Bonini M, et al., Beta₂-agonists for exercise-induced asthma, *Cochrane Database Syst Rev*. 2013 Oct 2;10

⁵ <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071648.pdf>

Table 1. Key Design Features of Clinical Studies in the Development Program

Study	Study Location	Subjects Randomized (n)	Dosing	Study Design	Primary Objective
ABS-AS-101	USA	47	A-MDPI PA-HFA	Phase 1, comparative, cumulative single-dose study in subjects with persistent asthma	Comparison of PK/PD, safety, efficacy of A-MDPI vs. PA-HFA after cumulative dose of 1440 mcg
ABS-AS-201	USA	72	A-MDPI PA-HFA	Phase 2, single-dose, dose-ranging study in subjects with persistent asthma	Assess PK/PD, efficacy and safety of 2 doses of A-MDPI vs. PA-HFA
ABS-AS-301	USA	158	A-MDPI PBO-MDPI	Phase 3, 12-wk, MC, R, DB, PC, repeat dose, parallel group study in subjects with persistent asthma	Assess efficacy and safety of A-MDPI vs. PBO-MDPI
ABS-AS-302	USA	38	A-MDPI PBO-MDPI	Phase 3, single-dose, R, DB, PC, 2-treatment, 2-sequence, 2-way crossover study in subjects with exercise-induced asthma	Assess efficacy and safety of A-MDPI vs. PBO-MDPI
ABS-AS-304	USA	160	A-MDPI PBO-MDPI	Phase 3, 12-wk, MC, R, DB, PC, repeat dose, parallel group study in subjects with persistent asthma	Assess efficacy and safety of A-MDPI vs. PBO. PK sub-study.
ABS-AS-306	USA	331	A-MDPI PBO-MDPI	Phase 3, 12-week, R, DB, PC, repeat dose, parallel group study in subjects with persistent asthma. TERMINATED EARLY.	Assess efficacy and safety of A-MDPI vs. PBO over 52-wks
ABS-AS-307	USA	337	A-MDPI	Phase3, DB, PC, 12-wk treatment with 40-wk OL, active treatment only study in subjects with persistent asthma	Assess safety of A-MDPI over 52-wks
ABS-AS-308	USA	345	A-MDPI	Phase 3, OL study over 36 or 50 days	Assess A-MDPI performance of device with dose counter with patients

Source: Adapted from Dr. Hull's primary clinical review, Table 2, A-MDPI: Albuterol MDPI; PA-HFA: ProAir HFA; PBO: placebo; PK: pharmacokinetics; PD: pharmacodynamics

3. CMC/Device

Primary Product Quality Reviewer: Yong Hu, Ph.D.

Acting CMC Lead: Craig Bertha, Ph.D.

The active component of ProAir RespiClick is albuterol sulfate. Of note, while multiple single-ingredient albuterol sulfate inhalation aerosols have been approved in the US, there are no inhalation dry powder albuterol products. The device for this combination product is a reservoir type (device-metered) of inhalation powder product.

Formulation

Albuterol MDPI Inhalation Powder product contains a formulation of albuterol sulfate and lactose monohydrate, delivering 108 mcg of albuterol sulfate (equivalent to 90 mcg of albuterol base) from the inhaler mouthpiece at each actuation. This formulation was used in the core clinical trials supporting the current application.

Each inhaler contains 0.65g of the formulation and provides 200 actuations. The device meters 117 mcg and delivers 108 mcg of albuterol sulfate from the mouthpiece (equivalent to 90 mcg of albuterol base). However, the labeled strength of the product corresponds to the

metered dose, i.e. 117 mcg, not the amount of drug emitted from the mouthpiece (108 mcg) which may appear discrepant versus the albuterol inhalation aerosol products on the market (inhalation aerosol strength is based on the amount of drug emitted from the mouthpiece). The strength and emitted dose will be clearly outlined in the labeling.

Dosage and Administration

Albuterol MDPI Inhalation Powder is recommended for oral inhalation only:

- For prevention of bronchospasm in adults and adolescents age 12 and older, 2 inhalations every 4 to 6 hours. In some patients, 1 inhalation every 4 hours may be sufficient.
- For prevention of exercise-induced bronchospasm in adults and adolescents age 12 and older, 2 inhalations 15 to 30 minutes before exercise

As the use of the device differs from the use of other albuterol “press-and-breathe” metered-dose inhalers (MDIs), the Dosage and Administration provides specific instructions on priming, use of spacer, cleaning, and discarding the device.

Of note, the Albuterol MDPI device resembles physically the marketed albuterol metered dose inhalers (MDIs). The MDIs can be used with a spacer device for pediatric patients; however, the Albuterol MDPI is not intended to be used with a spacer. To mitigate the risk of parents trying to use the Albuterol MDPI with a spacer, and potentially underdosing the patient, the labeling includes clear instructions that Albuterol MDPI should not be used with a spacer or volume holding chamber.

Device/Container Closure System

Albuterol MDPI is a reservoir type, inspiratory flow driven multi-dose dry powder inhaler containing albuterol sulfate blended with lactose monohydrate as the sole excipient. The design is based on (b) (4) and is operated by the patient as follows:

- The patient holds the device in an upright position,
- The patient opens the mouthpiece cover fully, exhales, places the mouthpiece between the lips, inhales forcefully and deeply, and removes the inhaler from his/her mouth,
- The patient then holds his/her breath for ten seconds, or as long as comfortably possible,
- The patient finally breathes out slowly and then closes the mouthpiece cover.

A dose counter decrements each time a dose is taken. Each inhaler device will be manufactured with (b) (4) doses but labeled as 200 doses to help insure that patients do not inadvertently deplete their inhaler. The inhaler does not lock when the counter reaches a reading of zero.

Three versions of the Albuterol MDPI device were used in the clinical program:

- (b) (4) was used in the first IVAX Spiromax studies outside the USA (Studies IX-100-076 and IX-101-076) which delivered 100 mcg albuterol sulfate
- (b) (4) was used in the supportive studies ABS-AS-101, ABS-AS-201, and ABS-AS-306

- (b) (4) was used in the pivotal safety studies in asthma: ABS-AS-301, -304 and -307. The applicant identified a problem with the (b) (4) device during Study ABS-AS-306 involving patients repeatedly opening and closing the mouthpiece cover of the device without inhaling following opening of the mouthpiece cover. This resulted in device failures during the study. Consequently, the applicant redesigned the device, (b) (4) which was used in the pivotal phase 3 studies. Additionally, the (b) (4) device reliability was evaluated in Study ABS-AS-308 discussed in Safety section below. The (b) (4) device is proposed for commercialization.

Based on the testing at various orientations and conditions, as well as in- and out-of-package testing, the applicant has proposed (b) (4) months expiry for the packaged product and 13 months expiry for the out-of- package product. However, the CMC team recommends and expiration dating period of 36 months.

The drug substance is manufactured by (b) (4) and (b) (4). The final drug product is manufactured by Teva Pharmaceutical Industries, Ltd., Israel. As of the time of this review, the Office of Regulatory Affairs (ORA) inspections have found all the inspected facilities acceptable.

The CMC review team has recommended approval of this NDA, and I concur with the recommendation.

4. Nonclinical Pharmacology/Toxicology

Primary Pharmacology/Toxicology Reviewer: Nikunj Patel, Ph.D.
Pharmacology/Toxicology Supervisor: Marcie Wood, Ph.D.

The following is adapted from Dr. Patel's review:

No nonclinical pharmacology or toxicology studies were conducted with the proposed product. For this NDA, the applicant is relying on demonstration of safety and efficacy from NDAs of previously approved albuterol products. Albuterol sulfate has been used clinically to treat bronchoconstriction related to asthma for decades and has a well-characterized pharmacological mechanism and safety profile. The applicant's Albuterol MDPI provides a new delivery system for patients at the same dosage as that proven safe and effective in other products, e.g., ProAir HFA; however, no new safety signals were identified regarding the drug substance or container-closure system extractable/leachable profile. The proposed active pharmaceutical ingredient is the same as ProAir HFA except that the HFA134a propellant and ethanol excipients have been replaced with lactose monohydrate. The proposed doses of the active ingredient, albuterol sulfate, are similar to the already approved doses, there are no novel excipients, and the impurities are within acceptable limits. The applicant provided a summary of publicly available literature on the nonclinical assessment for safety of albuterol and is referencing nonclinical information from previously approved albuterol products. The nonclinical studies in rat and dog conducted in support of approved albuterol sulfate products have shown that the cardiovascular system is a major target organ. Clinically relevant cardiovascular toxicities observed in nonclinical studies include hypotension, tachycardia, changes in ECG wave parameters, and myocardial necrosis.

The pertinent labeling language proposed by the applicant mirrors the ProAir HFA (NDA 21,457), labeling language. The pharmacology/toxicology review team recommends minor revisions for consistency with the current labeling practices and I agree.

The pharmacology/toxicology review team concluded that the data in this submission were adequate to support approval of the NDA from a nonclinical perspective and I agree.

5. Clinical Pharmacology/Biopharmaceutics

Clinical Pharmacology Primary Reviewer: Yunzhao Ren, Ph.D.

Clinical Pharmacology Team Leader: Satjit Brar, Pharm D., Ph.D.

The following is adapted from Dr. Ren's review.

Key Findings

The clinical pharmacology program in support of the NDA included pharmacokinetic (PK) and pharmacodynamic (PD) data and PK-PD relationships from:

- Study ABS-AS-101 was a phase 1, multi-center, randomized, double-blind, double-dummy, cumulative dose, two-period, crossover study in subjects with persistent asthma to assess efficacy, PK and extra-pulmonary PD responses following 1440 mcg albuterol cumulative dose (administered as 1+1+2+4+8 inhalations of 90 mcg per inhalation) delivered via either Albuterol MDPI or ProAir HFA within 2 hours.
- Study ABS-AS-201 was a phase 2, dose-ranging, multicenter, randomized, double-blind, double-dummy, single-dose, 5-treatment, 10-sequence, placebo-controlled, crossover study comparing the bronchodilator response to Albuterol MDPI and ProAir HFA at two dose levels (90 mcg and 180 mcg) in subjects with persistent asthma.
- Study ABS-AS-304 was a phase 3, 12-week, multicenter, randomized, double-blind, placebo-controlled, repeat-dose, parallel-group study to evaluate the efficacy and safety of Albuterol MDPI relative to Placebo MDPI in subjects with persistent asthma.

The key findings from the above studies are:

- 1) Albuterol systemic exposure was similar between Albuterol MDPI and ProAir HFA following cumulative dose (1440 mcg in total) inhalation. The ratios (Albuterol MDPI /ProAir HFA) of AUC_{0-t} and C_{max} were 1.11 (90% CI = 1.04, 1.19) and 1.34 (90% CI = 1.17, 1.53), respectively.
- 2) Following 180 mcg single dose inhalation, mean AUC_{0-t} and C_{max} of albuterol were 2147 (CV = 35.5%) pg*hr/mL and 325 (CV = 37.6%) pg/mL, respectively. The median T_{max} was approximately half an hour (range from ~10 minutes to ~5 hour). The steady state was reached following one week of QID dosing. The accumulation ratio of AUC₀₋₆ was 1.7.
- 3) Some key efficacy PD responses were similar between Albuterol MDPI and ProAir HFA following 180 mcg single dose inhalation. The percentage of responders (15% increase in FEV₁ from baseline) was 63% and 52% for Albuterol MDPI and HFA, respectively. The median onset time for responders

was 6 minutes for both products. The median times to peak FEV1 were 46.5 and 43.5 minutes for Albuterol MDPI and HFA, respectively. The mean durations of respond were 3.1 hour and 3.0 hour for Albuterol MDPI and HFA, respectively. These results were generally consistent with the approved label for NDA 021457 ProAir HFA.

- 4) The effects of albuterol on extra-pulmonary PD responses (i.e., systolic blood pressure, diastolic blood pressure, heart rate, QTc interval, and plasma glucose and potassium concentrations) were similar between Albuterol MDPI and the approved ProAir HFA following cumulative dose inhalation in study ABS-AS-101. Although some differences were statistically significant, they were numerically small and are not considered to be clinically meaningful.

Dose Selection

The clinical program has utilized previously approved albuterol doses as the clinically relevant doses with acceptable risk-benefit profile have been well characterized for the active ingredient albuterol sulfate. The current submission provided limited data to analyze for a dose-dependent relationship of adverse events using therapeutic doses of Albuterol MDPI. Review of Study ABS-AS-201, which administered doses of Albuterol MDPI 90 mcg and 180 mcg, did not demonstrate a correlation between drug dose and increased adverse events.

Conclusion

The clinical pharmacology team concluded that the information submitted was adequate to support approval of the NDA from their perspective and I agree. The clinical pharmacology review team recommended revisions to the proposed labeling for consistency with the ProAir HFA labeling and the current labeling practices and I agree.

6. Clinical Microbiology

Microbiology Reviewer: Bryan S. Riley, Ph.D.

Senior Review Microbiologist: John W. Metcalfe, Ph.D.

The microbiology team recommends that the application be approved from their perspective and I concur.

7. Clinical/Statistical – Efficacy

Primary Clinical Reviewer: Keith Hull, M.D., Ph.D.

Primary Statistical Reviewer: Robert Abugov, Ph.D.

Statistical Team Leader: David Petullo, M.S.

The primary evidence of efficacy in this submission was derived from five studies. Studies ABS-AS-101, -201, -301, and -304 evaluated the product in patients with persistent asthma and study ABS-AS-302 evaluated the product in patients with exercise-induced bronchoconstriction (EIB). Although studies ABS-AS-101 and -201 were technically

pharmacokinetic/pharmacodynamic studies, their results directly pertain to the clinical activity of the active moiety, albuterol sulfate and are discussed in this section. The endpoints used in the clinical studies supporting efficacy, are similar to the endpoints used in the regulatory approval of other albuterol inhalation aerosol programs and are consistent with the regulatory precedent and previous advice by the Division.

Overview of Study Design and Conduct

Study ABS-AS-101:

A phase 1, multicenter (eight sites throughout the US), randomized, double-blind, double-dummy, cumulative-dose, crossover study in adult subjects (18 to 45 years of age) with persistent asthma. The primary objective of the study was to compare the efficacy of inhaled albuterol MDPI and inhaled ProAir HFA after a cumulative dose of 1440 mcg administered as 1+1+2+4+8 inhalations of 90 mcg per inhalation, given at intervals of 30 minutes. After an initial screening visit, subjects entered a Run-in Period of 7 to 14 days prior to their first of two treatment visits that were separated by 3 to 14 days of washout. A final follow-up visit was performed 1 to 5 days after subjects' last treatment visit. The applicant's statistical analysis plan intended to determine non-inferiority between the products. The primary efficacy endpoint of the study was the baseline-adjusted FEV₁ at 30 minutes after each of the five cumulative doses. Major secondary PD endpoints included change from baseline in short-term PD endpoints, including plasma potassium 15 minutes after each cumulative dose; change from baseline in heart rate 15 minutes after each cumulative dose; change from baseline in plasma glucose 15 minutes after each cumulative dose; and changes in QTc as determined from serial ECGs. A total of 47 subjects randomized (intent to treat population) and a subset of 24 subjects were randomized to the PK sub-study. Analysis populations were pre-defined and subsequently re-defined post-unblinding due to issues uncovered in review of PK data. Specifically, all the data from a single site were excluded from analyses for efficacy and PD/PK due to data from four subjects who had an insufficient number of samples and/or high pre-dose albuterol levels. The post-unblinding populations were used for all efficacy, PD, and PK analyses in this study. The exclusion of data from the single site was assessed by the primary review team and deemed to be unlikely to affect interpretation of results. Overall, baseline demographics and disease characteristics were comparable between the treatment arms. While the study was conducted as designed, the FDA statistical review team identified several methodological issues with the applicant's statistical analysis, including (1) control of type 1 error for the five primary endpoints was inadequate as there was no pre-specified testing hierarchy; (2) the planned statistical comparison, non-inferiority of Albuterol MDPI to HFA, was based on a non-inferiority margin which was not adequately justified. Therefore, the results from study ABS-AS-101 were considered descriptive by the FDA statistical review team.

Study ABS-AS-201:

A dose-ranging, phase 2, multicenter, randomized, double-blind, double-dummy, single-dose, five-treatment, 10-sequence, placebo-controlled, crossover comparison of the bronchodilator response to Albuterol MDPI and ProAir HFA in male and female subjects 12 years of age and older with persistent asthma. The primary objective of the study was to assess the efficacy of two doses of albuterol delivered as either Albuterol MDPI or ProAir HFA compared to placebo. The primary efficacy endpoint of the study was the baseline-adjusted area under the

effect curve (AUEC) for FEV₁ observed up to 6 hours following completion of dosing (FEV₁ AUEC_{0-6h}) measured in L*hr. The planned statistical tests compared each active treatment group to placebo. There were no statistical tests pre-specified to compare the different albuterol doses or between the two devices. A total of 72 subjects were randomized. Baseline demographics and disease characteristics, and prior/concomitant therapies were comparable between the treatment arms. Protocol violations were small with 1 subject being excluded from analyses due to enrollment at more than one site.

Studies ABS-AS-301:

A phase 3, 12-week, multicenter, randomized, double-blind, placebo-controlled, repeat-dose, parallel-group study to evaluate the efficacy and safety of Albuterol MDPI compared to Placebo MDPI in male and female subjects 12 years of age and older with persistent asthma. The primary objective of the study was to assess the overall efficacy and safety of Albuterol administered via MDPI compared to Placebo over a 12-week period in subjects diagnosed with persistent asthma and on a stable dose of inhaled corticosteroids. The primary efficacy endpoint of the study was the baseline-adjusted area under the effect curve (AUEC) for FEV₁ observed up to six hours following completion of dosing (FEV₁ AUEC_{0-6h}) measured in L*hr over the 12-week treatment period. A total of 158 subjects, of whom 30 between 12 and 17 years of age, were equally randomized to placebo and Albuterol MDPI with 79 subjects in each treatment arm. Baseline demographics and disease characteristics, and prior/concomitant therapies were comparable between the treatment arms. A total of six subjects discontinued the study, five subjects on placebo, and one on Albuterol MDPI. There was one protocol violation in the placebo MDPI arm.

Study ABS-AS-304:

A phase 3, 12-week, multicenter, randomized, double-blind, placebo-controlled, repeat-dose, parallel-group study to evaluate the efficacy and safety of Albuterol MDPI compared to placebo MDPI in male and female subjects 12 years of age and older with persistent asthma. The primary objective of the study was to assess the overall efficacy and safety of Albuterol administered via MDPI compared to placebo over a 12-week period in subjects diagnosed with persistent asthma and on a stable dose of inhaled corticosteroids. The primary efficacy endpoint of the study was the baseline-adjusted area under the effect curve (AUEC) for FEV₁ observed up to 6 hours following completion of dosing (FEV₁ AUEC_{0-6h}) measured in L*hr over the 12-week treatment period. A total of 160 subjects, of whom 31 between 12 and 17 years of age, were equally randomized to placebo and Albuterol MDPI. Baseline demographics and disease characteristics, and prior/concomitant therapies were comparable between the treatment arms. A total of 13 (8%) subjects discontinued the study, seven (8%) on placebo, and six (8%) on Albuterol MDPI. Protocol violations were small with a total of 2 (1%) violations.

Studies ABS-AS-301 and -304, of similar design and conduct, were used to support the efficacy and safety of Albuterol MDPI at the proposed recommended dosing in patients with persistent asthma, one of the two proposed clinical indications for this application. These studies also comprise the majority of the safety database as discussed in Section 8 below. The proportion of patients between 12 and 17 years of age is approximately 20% in both studies, which is sufficient to provide a reasonable assessment of efficacy and safety on this patient population to support the proposed indications down to 12 years of age.

Study ABS-AS-302:

A phase 3, single-dose, randomized, double-blind, placebo-controlled, two-treatment, two-sequence, two-way crossover, multicenter study that compared Albuterol MDPI to placebo MDPI in male and female subjects 12 to 50 years of age with a documented history of exercise-induced asthma defined as at least 20% decrease from pre-exercise FEV₁. The primary objective of the study was to assess the efficacy of a single-dose (two inhalations) of Albuterol MDPI 90 mcg/inhalation compared to placebo MDPI in subjects experiencing exercise-induced bronchoconstriction, the second of the two proposed clinical indications for this application. The primary efficacy endpoint was the maximum percentage fall from baseline in FEV₁ observed up to 60 minutes post-exercise challenge. A total of 38 subjects were randomized with 19 subjects in each treatment arm. Protocol violations were small with a total of 2 subjects.

Efficacy Results

- The efficacy data supporting the proposed indication “Treatment or prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease” are summarized below for each study individually:

Study ABS-AS-101

The primary efficacy endpoint, the baseline-adjusted FEV₁ at 30 minutes after each of the five cumulative doses, demonstrated the effectiveness of both albuterol products as summarized in Table 2 below. The observed differences between the two products ranging between 36 mL to 66 mL are not considered clinically meaningful.

Table 2. Study ABS-AS-101: ΔFEV₁ after Cumulative Dosing*

Cumulative Dose (mcg)	ΔFEV ₁ mL (N)		Treatment Difference (90% CI)
	HFA	MDPI	HFA – MDPI
90	426 (46)	383 (46)	43 (-25, 110)
180	505 (45)	439 (46)	66 (-2, 133)
360	573 (46)	528 (46)	45 (-22, 112)
720	611 (46)	563 (46)	48 (-19, 115)
1440	649 (45)	613 (46)	36 (-31, 103)

*Source: Adapted from Dr. Abugov’s Statistical Review, Table 5. HFA: ProAir HFA; MDPI: Albuterol MDPI

Study ABS-AS-201

The primary efficacy endpoint, the baseline-adjusted FEV₁ AUEC_{0-6hr} measured in L*hr, demonstrated significant increases in subjects treated with any dose of Albuterol MDPI or ProAir HFA compared to placebo-treated subjects. The results summarized in Table 3 below confirm the efficacy of albuterol using either of the tested devices, in subjects with asthma. A dose-response was observed within treatment arms but not statistically significant. Time to onset of action, approximately five minutes after dosing, was similar in the MDPI and the

HFA product. As discussed in the *Overview of Study Design and Conduct* above, the study was not designed to provide substantial support for comparative efficacy between the two devices, and statements on device comparability as proposed by the applicant are inaccurate and not justified for inclusion in the labeling.

Table 3. Study ABS-AS-201: Δ FEV₁ AUC_{0-6hr}*

Treatment Arm	Δ AUC _{0-6hr} L*hr (N)	Treatment Difference Drug-Placebo (p-value)
Placebo	0.244 (69)	-
Albuterol-MDPI 90 mcg	1.214 (68)	0.970 (<.0001)
ProAir-HFA 90 mcg	1.124 (70)	0.88 (<.0001)
Albuterol-MDPI 180 mcg	1.394 (68)	1.15 (<.0001)
ProAir-HFA 180 mcg	1.328 (68)	1.083 (<.0001)

*Source: Adapted from Dr. Abugov's Statistical Review, Table 8; HFA: ProAir HFA; MDPI: Albuterol MDPI

Studies ABS-AS-301 and -304

Both studies met their primary efficacy endpoint, baseline-adjusted Δ FEV₁ AUC_{0-6hr} measured in L*hr over the 12-weeks. Subjects treated with Albuterol MDPI 180 mcg demonstrated significant increases that were considered clinical meaningful when compared to placebo-treated subjects, summarized in Table 4.

Table 4. Studies ABS-AS-301, -304: Δ FEV₁ AUC_{0-6hr} Over 12 Weeks*

Study	Δ AUC _{0-6hr} L*hr (N)		Treatment Difference (p-value)
	Albuterol-MDPI 180 mcg (n)	PBO (n)	
ABS-AS-301	1.107 (78)	0.28 (79)	0.827 (<.0001)
ABS-AS-304	1.300 (75)	0.384 (84)	0.917 (<.0001)

*Source: Adapted from Dr. Abugov's Statistical Review, Table 14; HFA: MDPI: Albuterol MDPI

Consistent with, and supportive of the primary endpoint, secondary landmark analyses at Day 1 (Visit 1), Day 8 (Visit 2), and Day 85 (Visit 6), of baseline-adjusted Δ FEV₁ AUC_{0-6hr} were also statistically different between the Albuterol MDPI and placebo as shown in Table 5.

Table 5. Studies ABS-AS-301, -304: Δ FEV₁ AUC_{0-6hr}, by Study Day, Albuterol MDPI versus Placebo

Study	Visit	Δ AUC _{0-6hr} L*hr (N)		Treatment Difference Albuterol MDPI-Placebo	
		Albuterol MDPI	Placebo	Difference (p-value)	95% CI
301	Day 1	1.584 (78)	0.516 (79)	1.068 (<.0001)	(0.675, 1.460)
	Day 8	0.992 (78)	0.261 (78)	0.731 (<.0001)	(0.407, 1.055)
	Day 85	0.745 (77)	0.064 (77)	0.681 (<.0001)	(0.375, 0.986)
304	Day 1	1.633 (75)	0.581 (84)	1.053 (<.0001)	(0.56, 1.545)
	Day 8	1.146 (74)	0.374 (83)	0.772 (0.0004)	(0.352, 1.192)
	Day 85	1.122 (69)	0.196 (78)	0.926 (<.0001)	(0.57, 1.282)

*source: Adapted from the Division of Biometrics Statistical Review, Table 15

In Section 14 of the product labeling, the applicant proposed (b) (4) In addition, the applicant proposed inclusion of graphical representation of the Week 12 mean change in FEV₁ time-profile 0 to 6 hours post-dose from each study. The clinical and statistical review teams concluded that the efficacy data from this program should be presented in a manner consistent with the labeling of other albuterol inhalation aerosols in light of the similarity and development programs, endpoints used, and the familiarity of the prescribers with that format. Therefore, the teams recommended, and I concur, that the results from studies ABS-AS-301 and -304 should be presented consistent with ProAir HFA labeling as discussed in Section 12, Labeling, in this memorandum.

The applicant proposes inclusion of labeling statements in Section 14 based on analyses of data from pooled studies ABS-AS-301, and -304. These statements pertain to the onset of action (the median time to onset was between 5.4 and 5.7 minutes, and median duration of effect as measured by a 15% increase was approximately 2 to 3 hours), and the number of patients who achieved a 15% increase in FEV₁ within 30 minutes post dose on Day 1. Of note, these statements are based on analyses of pooled data from studies ABS-AS-301, and -304. Because these analyses were not pre-specified in the statistical analysis plan, Type I error was not controlled; the statistical review team recommended that these analyses were only exploratory and do not warrant inclusion in the product labeling. While the proposed labeling statements regarding these endpoints were based on exploratory analyses from pooled data, they are clearly in line with the know kinetics of the response of albuterol as described in the product labeling of other albuterol inhalation aerosol products. Therefore, I recommend that for consistency and level playing field, they are also described in this product's label.

- The efficacy data supporting the proposed indication “Prevention of exercise-induced bronchospasm in patients 12 years of age and older” are summarized for study ABS-AS-302:

In study ABS-AS-302, compared to placebo, two inhalations of Albuterol MDPI taken 30 minutes before exercise reduced maximum post-exercise decreases in FEV₁ (Table 5), and increased the percent of patients whose maximum post-exercise decrease in FEV₁ was less than 10% (Table 7). The applicant proposed (b) (4). However, the Division recommends that they follow what was done for the ProAir HFA program, which was to use 20%, as this is similar to the entry criteria for the study as summarized in Table 7. Therefore, the clinical and statistical review teams recommended, and I concur, that the results from study ABS-AS-302 should be presented consistent with ProAir HFA labeling as discussed in Section 12, Labeling, in this memorandum.

Table 6. Study ABS-AS-302: Maximum Exercise-Induced Percent Decrease in FEV₁

Treatment Arm	Max % Decrease FEV ₁ N=38	Treatment Difference Drug-Placebo (p-value)
Placebo	22	-
Albuterol MDPI 180 mcg	6	-16 (<.0001)

*Source: Adapted from Dr. Abugov’s Statistical Review, Table 17; HFA: MDPI: Albuterol MDPI

Table 7. Study ABS-AS-302: Percentage of Patients with Maximum Exercise Induced Percent Decrease in FEV₁ <10% and <20%

Treatment Arm	Percent Patients Protected N=38	Treatment Difference Drug-Placebo (p-value)
Maximum Exercise Induced Percent Decrease in FEV₁ <10%		
Placebo	16% (6/38)	-
Albuterol MDPI 180 mcg	84% (32/38)	68% (<.0001)
Maximum Exercise Induced Percent Decrease in FEV₁ ≤20%		
Placebo	42% (16/38)	-
Albuterol MDPI 180 mcg	97% (37/38)	55% (<.0001)

*Source: Adapted from Dr. Abugov’s Statistical Review, Table 18 and additional FDA statistical team analyses; MDPI: Albuterol MDPI

Overall, the study was conducted as planned and demonstrated a statistically significant and clinically meaningful benefit of Albuterol MDPI over placebo in preventing exercise-induced bronchospasm. Consistent with the principles outlined in the 2002 FDA Guidance for Industry: *Exercise-Induced Bronchospasm (EIB) – Development of Drugs to Prevent EIB*⁶, and the pre-submission Division's advice to applicant, the results from this single study provide sufficient evidence of efficacy to support the proposed indication.

- **Includes discussion of both the statistical reviewer review and the clinical efficacy review with explanation for CDTL's conclusions and ways that any disagreements were addressed.**

Both the clinical and statistical review teams are in agreement that there is adequate and substantial evidence of efficacy for Albuterol MDPI for the treatment or prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease and prevention of exercise-induced bronchospasm in patients 12 years of age and older.

- **Includes discussion of notable efficacy issues both resolved and outstanding**

No other notable efficacy issues or outstanding efficacy issues were identified.

8. Safety

- **Discuss the adequacy of the database, major findings/signals, special studies, foreign marketing experience, if any, and plans for postmarketing**

A total of 10 clinical studies in adult and adolescent patients have been completed and support the safety of Albuterol MDPI. Overall, 1456 patients were included in the clinical program of whom 1120 received treatment with Albuterol MDPI. Among patients treated with Albuterol MDPI, 840 were treated with the inhaler device proposed for marketing. The core safety data were derived primarily from studies ABS-AS-301, -304, and -307 given the overall study design, large subject cohorts, and placebo-controlled periods. Data from Studies ABS-AS-307 and -308 were used to assess the Albuterol MDPI device counter's reliability. Additional supportive safety information was derived from the cumulative dosing phase 1 study ABS-AS-101, and the PK/PD dose-ranging study ABS-AS-201. The studies were conducted entirely in the USA at geographically diverse locations. The safety database of the to-be-marketed drug-device combination is reasonable to support the adequate assessment of the risk:benefit profile of Albuterol MDPI.

The design features of studies ABS-AS-101, -201, -301 and -304 are described in Section 7 above.

Study ABS-AS-307:

A 52-week, multicenter (30 US study sites) study in subjects ages 12 years and older with a documented history of persistent asthma. The study consisted of two parts: Part 1 was a 12-

⁶ <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071648.pdf>

week double-blind treatment period in which subjects were randomized to receive two inhalations QID of either Albuterol MDPI or Placebo MDPI; and Part 2 was a 40-week open-label treatment period in which subjects received open-label Albuterol MDPI prn. The primary objective of the study was to assess the safety of Albuterol MDPI over 52 weeks during the two dosing periods. A major secondary objective was to evaluate the Albuterol MDPI device performance through both periods of the study. The focus of Study ABS-AS-307 was primarily evaluation of the device performance. Descriptive statistics were used to assess study variables and safety outcomes. A total of 337 subjects were randomized to either placebo MDPI (n=169) or Albuterol MDPI (n=168) with balanced disease and demographic characteristics, and prior/concomitant therapies between the two arms. A total of 13% of subjects discontinued the study (n=23 on placebo, n=22 on Albuterol MDPI) for comparable reasons. The protocol violations were small, 5 (3%) subjects on placebo, and 1 (<1%) subject on Albuterol MDPI resulting in discontinuation in 1 subject on placebo, and 1 on Albuterol MDPI.

Study ABS-AS-308:

A multicenter (30 US study sites), phase 3, open-label study in subjects aged 4 years and older who have been diagnosed with persistent asthma or chronic obstructive pulmonary disease. The primary objective of the study was to assess the performance of the Albuterol MDPI dose-counter with “typical” patient use. The primary endpoint of Study ABS-AS-308 assessed Dose Cycle “not count” given that it is the most clinically important dose counter discrepancy that may result in undercounting and patient running out of active treatment. Subjects with adequate MDPI device technique who were 90% compliant with dosing and diary completion of the previous 7 days of the run-in period were enrolled. Treatment consisted of Albuterol MDPI 90 mcg 2 puffs twice daily for approximately 50 days. Of the total of 317 subjects, 16 (5%) discontinued the study.

Safety data from Studies ABS-AS-301, -304, and the 12-week controlled period of Study ABS-AS-307 were pooled for the primary analysis of safety as these studies were of similar design and study population, and allowed for the direct comparison of adverse events between treatment with Albuterol MDPI (n=321) and placebo (n=333) in subjects using the to-be-marketed device.

Overall, the safety in this submission remains consistent with the safety of other albuterol inhalation aerosols available on the market for decades and no new safety signals have been identified. The major risks of albuterol include paradoxical bronchospasm, deterioration of asthma, and cardiovascular and metabolic effects mediated via albuterol’s beta-adrenergic agonistic properties are well characterized with the active moiety and are captured in the product labeling. The risks of Albuterol MDPI treatment in the target patient population appear to be qualitatively similar to those seen with other albuterol inhalation aerosols available on the market for decades and do not warrant post-marketing studies or Risk Evaluation and Mitigation Strategies (REMS).

- **General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests.**

Deaths

No deaths occurred during the clinical program for Albuterol MDPI.

Serious Adverse Events

A total of 15 subjects reported a serious adverse event (SAE) during the Albuterol MDPI development program (n=13 on Albuterol MDPI vs. n=2 on placebo MDPI). The overall incidence of SAEs was low and balanced between treatment groups during the controlled period of Studies ABS-AS-301, -304, and -307: a total of two of 321 Albuterol MDPI-treated subjects and one of 333 (<1%) Placebo MDPI-treated subjects reported a serious adverse event (enterocolitis and pharyngeal abscess, and first trimester spontaneous abortion, respectively). Two subjects in Study ABS-AS-308 (atrial fibrillation; rash) and two subjects in Study ABS-AS-306 (asthma; rectal adenocarcinoma) reported serious adverse events. A total of seven subjects experienced a serious adverse event during the open-label period of Study ABS-AS-307 that included a single case each of cellulitis, pancreatic carcinoma, gastrointestinal carcinoma, atrial fibrillation, papillary thyroid cancer, asthma, and kidney stone. The overall incidence and types of serious adverse events do not identify a new safety signal associated with the use of Albuterol MDPI.

Discontinuations due to Adverse Events

A total of 10 subjects discontinued from study treatment due to adverse events during the Albuterol MDPI development program (n=8 on Albuterol MDPI vs. n=2 on placebo MDPI). Majority of these events were also listed as the serious adverse events discussed above. The overall incidence and types of adverse events leading to discontinuation do not identify a new safety signal associated with the use of Albuterol MDPI.

Adverse Events of Special Interest

To assess adverse events potentially associated with the use of albuterol as a β_2 -agonist, the applicant evaluated all adverse events within the cardiac disorders, central nervous system, and vascular disorders System Organ Classes in conjunction with related preferred terms from the metabolism and nutritional disorders, psychiatric disorders, general conditions, and administrative disorders investigations, and musculoskeletal System Organ Classes. The incidence of all events of special interest was very low with only headache and sinus headache being reported $\geq 1\%$ of Albuterol MDPI-treated subjects. The changes from baseline in vital signs were small and similar between albuterol treatments (i.e. Albuterol MDPI, ProAir HFA) and not clinically meaningful. These changes are not unexpected given the underlying mechanism of action of albuterol. No new safety signals were identified.

Hypersensitivity reactions have been reported following the administration of albuterol sulfate presenting as urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema. In the Albuterol MDPI clinical program, four mild hypersensitivity reactions (urticaria (n=2), face swelling (n=1), pruritus (n=1)) were reported during the controlled periods of Studies ABS-AS-301, -304, or -307 in subjects treated with Albuterol MDPI. No reports of Albuterol MDPI-associated hypersensitivity reactions were reported during the open-label period of Study ABS-AS-307 or in the remainder of the applicant's studies. A single case of

anaphylaxis was reported in the Placebo MDPI treatment arm during Study ABS-AS-307. The case of anaphylaxis was attributed to lactose excipient and warrants inclusion in the labeling as discussed under subsection Special Safety Concern below.

Safety of Repeat Escalating Dosing

As described above, phase 1 study ABS-AS-101 compared five cumulative doses of Albuterol MDPI 90 mcg and ProAir HFA 90 mcg administered as 1+1+2+4+8 inhalations for a total albuterol dose of 1440 mcg to mimic a real-world clinical scenario where patients may repeatedly self-administer the product over a short period of time resulting in significant cumulative exposure and potential toxicity. The effects of albuterol on systolic blood pressure, diastolic blood pressure, heart rate, QTc interval, and plasma glucose and potassium concentrations were similar between Albuterol MDPI and the approved ProAir HFA following cumulative dose inhalation. Five adverse events related to laboratory measurements following treatment with either Albuterol MDPI or ProAir HFA were reported in four subjects: decreased serum potassium (n=2), increased serum potassium (n=1), increased bilirubin (N=1), and increased serum LDH (n=1). Abnormal laboratory values were similar between treatment arms and no clinical intervention was required to treat the abnormal laboratory values.

Laboratory Abnormalities

No hematology, clinical chemistry, or urinalysis assessments were performed in Studies ABS-AS-201, -301, -302, or -304. Study ABS-AS-307 analyzed blood samples at the screening visit, Week 12, and Week 52 (or early discontinuation). No clinically meaningful changes from baseline were identified during any period of the study. In the cumulative dose study ABS-AS-101, mean changes from baseline in hematology and clinical chemistry values were generally small and similar between treatment arms. No significant other laboratory abnormalities were noted in this submission.

- **Immunogenicity**

Not applicable.

- **Special safety concerns**

Anaphylaxis

A single case of anaphylaxis, attributed to the lactose excipient, was reported in the placebo MDPI treatment arm during Study ABS-AS-307. The risk of hypersensitivity, including anaphylaxis can be mitigated via labeling as a contraindication to subjects with severe hypersensitivity to milk proteins, and a statement in the Warnings and Precautions section of the product label.

Safety Related to the Device and Integrated Dose-Counter

The potential MDPI device-specific safety related issues pertain to the integrated dose counter and the risk of counter malfunction resulting in undercounting that can potentially mislead patients to think that there are remaining doses when in fact the canister is empty. To address this concern, the applicant conducted the designated study ABS-AS-308 described above. Subject-reported MDPI counter readings and subject-reported dose cycles recorded in the diaries were assessed and discrepancies were classified into the following categories: (1) dose

cycle not count (i.e., undercount), deemed most clinically relevant; (2) dose cycle over-count; (3) count unknown dose cycle; (4) count up unknown dose cycle; (5) total inhaler discrepancy size. Overall rate of inhaler discrepancies was ~5.1/200 dose cycles (in the per-protocol population) and 5.7/200 dose cycles (in the intent to treat population) with dose cycle over-count most common. The discrepancy rate for dose cycle undercount was low at 2.1/200 dose cycles. Study ABS-AS-307 also evaluated the Albuterol MDPI device performance throughout both periods of the study. Out of 672 placebo MDPI inhalers and 647 Albuterol MDPI inhalers used in the 12-wk DB period, and 1252 Albuterol MDPI inhalers used in the following OL phase of the study, six subjects reported a total of 7 broken inhalers (most due to unrelated physical damage), and 14 reported device malfunction which included inhaler abuse, exposure to extreme moisture, dose-counter errors. Two subjects reported perceived inadequate dose inhalation; however subsequent testing did not corroborate the finding. Overall, the device and dose-counter failure rates were low and the types of failure do not appear to indicate a systematic device flaw that may impact the safe or effective use of the device.

- **Discussion of primary reviewer's comments and conclusions**

Dr. Hull has concluded that the types and rates of adverse events submitted with this NDA are generally consistent with those of albuterol and has not identified any new safety signals. The safety profile of Albuterol MDPI appears to be consistent with the safety profile of approved albuterol inhalation aerosols and provides for an acceptable risk:benefit balance for the proposed indications.

- **Highlight differences between CDTL and review team with explanation for CDTL's conclusion and ways that the disagreements were addressed**

I concur that the safety profile, and risk:benefit balance, of Albuterol MDPI for the proposed indications is acceptable.

- **Discussion of notable safety issues (resolved or outstanding)**

Notable issues are described above. There are no outstanding safety issues.

9. Advisory Committee Meeting

No Advisory Committee meeting was convened for this NDA. No issues were identified warranting Advisory Committee input, as the safety and efficacy of Albuterol NDA was clear and substantial, with an acceptable safety profile that was consistent with the known safety profile of approved albuterol inhalation aerosols.

10. Pediatrics

- **Peds exclusivity board review - PPSR/WR**

Not applicable.

- **PeRC Review Outcome-PMCs, deferrals, waivers, pediatric plan, peds assessment**

The approval of Albuterol sulfate MDPI, as a new dosage form, triggers PREA. The applicant has an agreed initial pediatric study plan. To address the PREA requirements, the applicant has requested a partial waiver of requirements for pediatric studies in patients from birth to 3 years of age based on section 505B(a)(4)(B) of the Act stating that necessary studies of Albuterol MDPI in this age group are impossible or highly impracticable due to the nature of the drug-device delivery. The current standard of administration of albuterol in this patient population is via a nebulizer. Teva has also submitted a request for a deferral of the requirement to conduct pediatric studies in patients 4 to less than 12 years of age till after the adolescent and adult phase 1 and 2 studies had successfully demonstrated that systemic exposure and safety, efficacy and pharmacodynamic effects following administration of Albuterol MDPI in adolescents and adults were similar to ProAir HFA. The deferred pediatric studies are ongoing. The current application is for indications that include adolescent patients down to age 12 years of age for whom the pediatric assessment is complete. Of note, study ABS-AS-302 which provided the evidence of efficacy for the prevention of EIB, enrolled only two subjects in the adolescent age group, i.e. younger than 18 years of age. However, extrapolation of efficacy and safety for the prevention of EIB indication is justified based on several considerations, including (1) the condition of use is the same in all age ranges, (2) the effect of the active ingredient albuterol has been considered the same in all age ranges, (3) long-term safety of the Albuterol MDPI drug-device combination product has demonstrated in studies ABS-AS-301, and -304 in patients down to 12 years of age, and (4) similar approach of extrapolating safety and efficacy for this indication has been used for other albuterol inhalation aerosol products.

The Albuterol MDPI pediatric program was discussed at the Pediatric Review Committee (PeRC) meeting on January 7, 2015. The PeRC agreed with Division's recommendations to grant the above requests for a partial waiver of requirements for pediatric studies in patients from birth to 3 years of age and a deferral of the requirement to conduct pediatric studies in patients 4 to less than 12 years of age.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)**—Not applicable.
- **Exclusivity or patent issues of concern:**
 - With regards to patent certification, Teva has made a Paragraph IV certification to 3M's NDA 20503 for Proventil HFA. However, the 45 day period from Teva's patent certification notification to 3M coincides with the PDUFA goal date for this NDA, March 05, 2015 which may impact the timing of the regulatory action.
 - Teva Branded Pharmaceutical Products R&D, Inc. claims (b) (4) marketing exclusivity, in accordance with 21CFR 314.50(j) and with reference to 21 CFR 314.108(b)(4) for Albuterol Sulfate Inhalation Powder to treat or prevent bronchospasm in patients 12 years of age and older with reversible obstructive airway disease and for prevention of exercise-induced bronchospasm.

- **Financial disclosures**—Acceptable.
- **Other GCP issues**—Not applicable.
- **OSI audits**—None requested.
- **Other discipline consults**—None requested.
- **Any other outstanding regulatory issues**—None identified.

12. Labeling

- **Proprietary name**—No issues. The proposed proprietary name “ProAir RespiClick” has been found acceptable from both promotional and safety perspective by the Office of Prescription Drug Promotion (OPDP), the Division of Medical Error and Prevention Analysis, and the review team.
- **DDMAC, DMEPA and OSE Division comments**— Minor revisions were implemented for clarity and consistency.
- **Physician labeling**
Changes throughout the labeling for consistency with current labeling practices
Changes to Dosage Forms and Strengths:
 - Revise to clearly describe and explain the discrepancy with the already approved albuterol inhalation aerosols: as discussed in CMC/Device section aboveMajor changes with respect to Efficacy:
 - Revise Section 14 for consistency with ProAir HFA labeling as discussed in Clinical/Statistical - Efficacy section above:
 - Replace the two figures with two serial FEV1 curves over 6 hours: one for Day 1 and one for the last day of the trial (Day 85) from either Study 1 or Study 2.
 - Delete (b) (4)
 - Revised text to capture changes in the data presentation.
 - Replace (b) (4)
 - Remove (b) (4)
 - Remove (b) (4)
- **Carton and immediate container labels (if problems are noted)**—No issues. DMEPA found the proposed container labels, insert labeling, and instructions for use acceptable.
- **Patient labeling/Medication guide (if considered or required)**— Albuterol MDPI does not have a Medication Guide. Minor revisions were implemented to the patient labeling for clarity and consistency with the physician labeling and to improve readability.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

I recommend approval of this application, provided agreement can be reached with the applicant on revisions to the proposed label.

- **Risk Benefit Assessment**

Overview of Efficacy

The applicant aimed to develop Albuterol MDPI to be comparable to ProAir HFA such that both products delivered equivalent 90 mcg doses of albuterol base per device actuation with the intent that Albuterol MDPI could be dosed in the same manner as ProAir HFA.

Although not strictly designed to analyze for non-inferiority or comparability, the data from Studies ABS-AS-101 and -201 demonstrated similar single-dose efficacy and safety profiles of Albuterol MDPI and ProAir HFA in subjects age 12 years and older who were diagnosed with persistent asthma. Both studies met their primary endpoints assessing FEV₁ and analysis of the pharmacodynamic and pharmacokinetic parameters further supported a high degree of clinical similarity between Albuterol MDPI and ProAir HFA at each of the five doses. Additional analysis of the data did not demonstrate a difference in the onset of action of albuterol between either of the two products. Overall, these studies support the applicant's proposed dosing of Albuterol MDPI up to 180 mcg.

Studies ABS-AS-301 and -304 both met their primary endpoints demonstrating that subjects treated with Albuterol-MDPI 180 mcg experienced clinically meaningful and statistically significant increases in Δ FEV₁ AUC_{0-6hr} compared to placebo-treated subjects over the 12-weeks of the controlled period of the studies. Analyses of the secondary endpoints of both studies were supportive and together the data confirm the known effectiveness of albuterol in subjects with asthma.

Subjects treated with Albuterol-MDPI 180 mcg in Study ABS-AS-302 demonstrated a significant effect on exercise-induced bronchospasm compared to subjects treated with Placebo-MDPI. Treatment with Albuterol-MDPI prior to exercise reduced the post-exercise percentage fall in FEV₁ to 6% compared to 22% for placebo-treated subjects. An alternative way to put these findings into perspective is that 84% of Albuterol MDPI-pretreated subjects experienced a <10% decrease in FEV₁ compared to only 16% of placebo-pretreated subjects, which translates into a clinically significant benefit. Together, these data demonstrate a clinically meaningful benefit of Albuterol MDPI 180 mcg for patients diagnosed with exercise-induced bronchospasm.

Studies ABS-AS-307 and -308 were used to assess the performance of the new MDPI device. The performance of the MDPI device was a secondary objective in Study ABS-AS-307 and the primary objective of Study ABS-AS-308. The data from these studies demonstrated that the total number of device-related complaints was low and that the proposed MDPI device with integrated counter performed adequately and in a reliable manner with a minimal rate of dose cycle “undercounting”.

Overall, the data support the claim that pharmacologic therapy with Albuterol MDPI 180 mcg effectively treats and prevents bronchospasm in patients 12 years of age and older who are diagnosed with persistent asthma and/or exercise-induced asthma.

Overview of Safety

Albuterol has been in clinical use in the USA for over 30-years as a treatment for patients with acute asthma and as prophylaxis for exercise-induced bronchospasm. Consequently, the efficacy and safety of albuterol are well understood. Inhalation is the preferred route of delivery for patients with bronchospasm as it rapidly delivers a relatively low but effective dose of drug to the site of action. An added advantage of inhalation delivery is that the drug largely bypasses issues from drug metabolism and avoids many of the complications of systemic side effects.

A total of 10 clinical studies in adult and adolescent patients have been completed and support the safety of Albuterol MDPI. Overall, 1456 patients were included in the clinical program of whom 1120 received treatment with Albuterol MDPI. Among patients treated with Albuterol MDPI, 840 were treated with the inhaler proposed for marketing. The primary safety data is derived from clinical studies that were wholly conducted in the USA at geographically diverse locations.

No deaths occurred during the clinical program for Albuterol MDPI. A total of 15 subjects reported serious adverse events which included 13 subjects treated with Albuterol MDPI and two subjects treated with placebo. Similarly, only 10 subjects discontinued a clinical study due to an adverse event (Albuterol MDPI (n=8), Placebo MDPI (n=2)). The majority of the serious adverse events and adverse events resulting in discontinuation were not related to study drug. The most commonly reported adverse events (reported in $\geq 5\%$ of subjects) included upper respiratory tract infection, nasopharyngitis, and headache. In general, the percentage of subjects reporting adverse events was either similar between treatment arms or slightly greater in placebo-treated subjects. For labeling purposes, adverse events experienced $\geq 1\%$ of Albuterol MDPI-treated subjects and greater than placebo-treated subjects were back pain, pain, gastroenteritis, sinus headache, urinary tract infection.

Overall, analysis of the safety data did not demonstrate an important safety signal with the use of Albuterol MDPI and the results support the safety of Albuterol MDPI in the treatment or prevention of bronchospasm in patients 12 years of age and older with obstructive airway disease or exercise-induced bronchospasm.

Risk:Benefit Conclusions

The risk:benefit profile of Albuterol MDPI for the treatment or prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease and prevention of exercise-induced bronchospasm in patients 12 years of age and older is favorable. The risks of Albuterol MDPI treatment in this patient population appear to be qualitatively similar to those seen with other albuterol inhalation aerosols available on the market for decades.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies (REMS)**

The review of the current submission has not identified new serious safety concerns with Albuterol MDPI for use in the target patient population. Therefore a REMS is not required.

- **Recommendation for other Postmarketing Requirements and Commitments**

Overall, the safety in this submission remains consistent with the safety of other albuterol inhalation aerosols available on the market for decades, no new safety signals have been identified. The major risks of albuterol include paradoxical bronchospasm, deterioration of asthma, and cardiovascular and metabolic effects mediated via albuterol's beta-adrenergic agonistic properties are well characterized with the active moiety and are captured in the product labeling. The risks of Albuterol MDPI treatment in the target patient population appear to be qualitatively similar to those seen with other albuterol inhalation aerosols available on the market for decades and do not warrant post-marketing studies.

- **Recommended Comments to Applicant—None.**

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/s/

NIKOLAY P NIKOLOV
02/11/2015