CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-983/S009

Trade Name: Ventolin HFA

Generic Name: (albuterol sulfate HFA inhalation aerosol)

Sponsor: GlaxoSmithKline.

Approval Date: April 19, 2005

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APPLICATION NUMBER:

20-983/S009

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-983/S009

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-983/S-009

GlaxoSmithKline
P.O. Box 13398
Five Moore Drive
Research Triangle Park
North Carolina 27709-3398

Attention: Robert J. Bohinski
Associate Director, Respiratory US Regulatory Affairs

Dear Mr. Bohinski:

Please refer to your supplemental new drug application dated December 17, 2004, received December 20, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ventolin HFA (albuterol sulfate) Inhalation Aerosol.

We acknowledge receipt of your submissions dated December 21, 2004, February 23, March 18, and 25, and April 8, and 13, 2005.

This supplemental new drug application provides for Ventolin HFA MDI with dose counter.

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

The final printed labeling (FPL) must be identical to the enclosed labeling (package insert, patient instructions for use, and immediate container and carton labels submitted April 13, 2005).

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 20-983/S-009**." Approval of this submission by FDA is not required before the labeling is used.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Pulmonary and Allergy Drug Products and two copies of both the promotional materials and the package insert(s) directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

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

We remind you of your agreement listed in your amendment dated March 25, 2005, to complete the following within 18 months of approval:

Conduct a comprehensive and well-designed study of the dosing behavior of the Ventolin HFA product to fully characterize the observed high initial doses obtained during the priming actuations. The study should also address the impact of storage time (e.g., up to 9 months) and orientation on the dosing behavior during priming.

If you have any questions, call Akilah Green, Regulatory Project Manager, at (301) 827-5585.

Sincerely,

Richard Lostitto, Ph.D.
Chemistry Team Leader
Division of Pulmonary and Allergy Drug Products, HFD-570
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

Enclosure

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

/s/

Richard Lostritto

4/19/05 03:48:31 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-983/S009

LABELING

PRESCRIBING INFORMATION

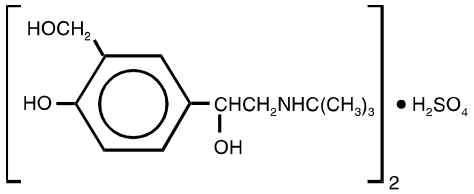
VENTOLIN® HFA

(albuterol sulfate HFA inhalation aerosol)

Bronchodilator Aerosol
For Oral Inhalation Only

DESCRIPTION

The active component of VENTOLIN HFA (albuterol sulfate HFA inhalation aerosol) is albuterol sulfate, USP, the racemic form of albuterol and a relatively selective beta$_2$-adrenergic bronchodilator. Albuterol sulfate has the chemical name α^1-[(*tert*-butylamino)methyl]-4-hydroxy-*m*-xylene-α, α′-diol sulfate (2:1)(salt) and the following chemical structure:



Albuterol sulfate is a white crystalline powder with a molecular weight of 576.7, and the empirical formula is $(C_{13}H_{21}NO_3)_2 \bullet H_2SO_4$. It is soluble in water and slightly soluble in ethanol.

The World Health Organization recommended name for albuterol base is salbutamol.

VENTOLIN HFA is a pressurized metered-dose aerosol unit fitted with a counter. VENTOLIN HFA is intended for oral inhalation only. Each unit contains a microcrystalline suspension of albuterol sulfate in propellant HFA-134a (1,1,1,2-tetrafluoroethane). It contains no other excipients.

Priming VENTOLIN HFA is essential to ensure appropriate albuterol content in each actuation. To prime the inhaler, release 4 test sprays into the air away from the face, shaking well before each spray. The inhaler should be primed before using it for the first time, when it has not been used for more than 2 weeks, or when it has been dropped.

After priming, each actuation of the inhaler delivers 120 mcg of albuterol sulfate, USP in 75 mg of suspension from the valve and 108 mcg of albuterol sulfate, USP from the mouthpiece (equivalent to 90 mcg of albuterol base from the mouthpiece).

Each 18-g canister provides 200 inhalations.

This product does not contain chlorofluorocarbons (CFCs) as the propellant.

CLINICAL PHARMACOLOGY

Mechanism of Action: In vitro studies and in vivo pharmacologic studies have demonstrated that albuterol has a preferential effect on beta$_2$-adrenergic receptors compared with isoproterenol. While it is recognized that beta$_2$-adrenergic receptors are the predominant receptors in bronchial smooth muscle, data indicate that there is a population of beta$_2$-receptors in the human heart

existing in a concentration between 10% and 50% of cardiac beta-adrenergic receptors. The precise function of these receptors has not been established (see WARNINGS: Cardiovascular Effects).

Activation of $beta_2$-adrenergic receptors on airway smooth muscle leads to the activation of adenylcyclase and to an increase in the intracellular concentration of cyclic-3′,5′-adenosine monophosphate (cyclic AMP). This increase of cyclic AMP leads to the activation of protein kinase A, which inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in relaxation. Albuterol relaxes the smooth muscles of all airways, from the trachea to the terminal bronchioles. Albuterol acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges. Increased cyclic AMP concentrations are also associated with the inhibition of release of mediators from mast cells in the airway.

Albuterol has been shown in most controlled clinical trials to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than isoproterenol at comparable doses while producing fewer cardiovascular effects. Controlled clinical studies and other clinical experience have shown that inhaled albuterol, like other beta-adrenergic agonist drugs, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes.

Preclinical: Intravenous studies in rats with albuterol sulfate have demonstrated that albuterol crosses the blood-brain barrier and reaches brain concentrations amounting to approximately 5.0% of the plasma concentrations. In structures outside the blood-brain barrier (pineal and pituitary glands), albuterol concentrations were found to be 100 times those in the whole brain.

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

Propellant HFA-134a is devoid of pharmacological activity except at very high doses in animals (380 to 1,300 times the maximum human exposure based on comparisons of AUC values), primarily producing ataxia, tremors, dyspnea, or salivation. These are similar to effects produced by the structurally related CFCs, which have been used extensively in metered-dose inhalers.

In animals and humans, propellant HFA-134a was found to be rapidly absorbed and rapidly eliminated, with an elimination half-life of 3 to 27 minutes in animals and 5 to 7 minutes in humans. Time to maximum plasma concentration (T_{max}) and mean residence time are both extremely short, leading to a transient appearance of HFA-134a in the blood with no evidence of accumulation.

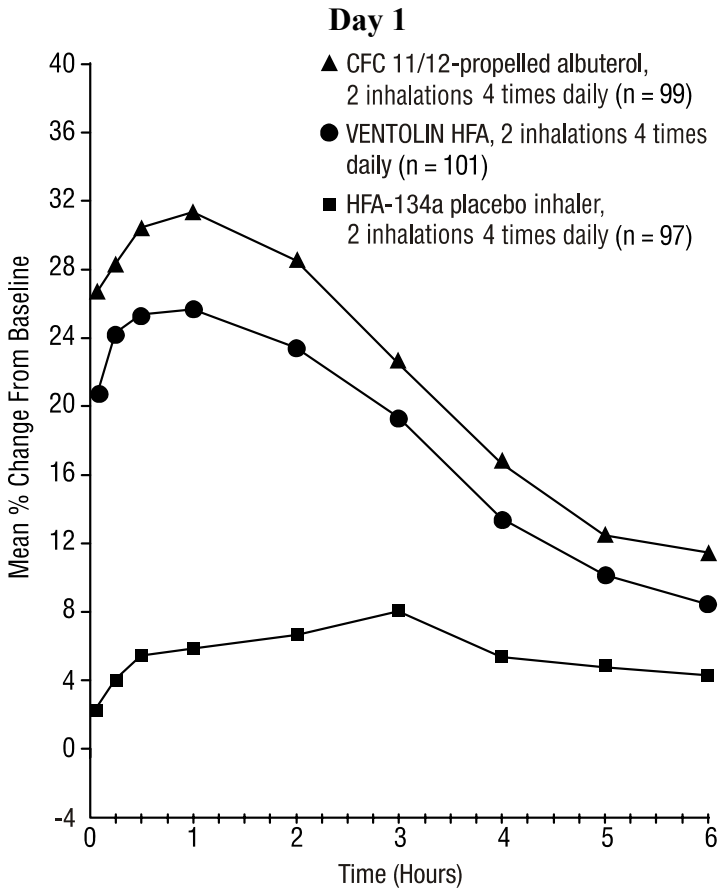
Pharmacokinetics: The systemic levels of albuterol are low after inhalation of recommended doses. A study conducted in 12 healthy male and female subjects using a higher dose (1,080 mcg of albuterol base) showed that mean peak plasma concentrations of approximately 3 ng/mL occurred after dosing when albuterol was delivered using propellant HFA-134a. The mean time

to peak concentrations (T_{max}) was delayed after administration of VENTOLIN HFA (T_{max} = 0.42 hours) as compared to CFC-propelled albuterol inhaler (T_{max} = 0.17 hours). Apparent terminal plasma half-life of albuterol is approximately 4.6 hours. No further pharmacokinetic studies for VENTOLIN HFA were conducted in neonates, children, or elderly subjects.

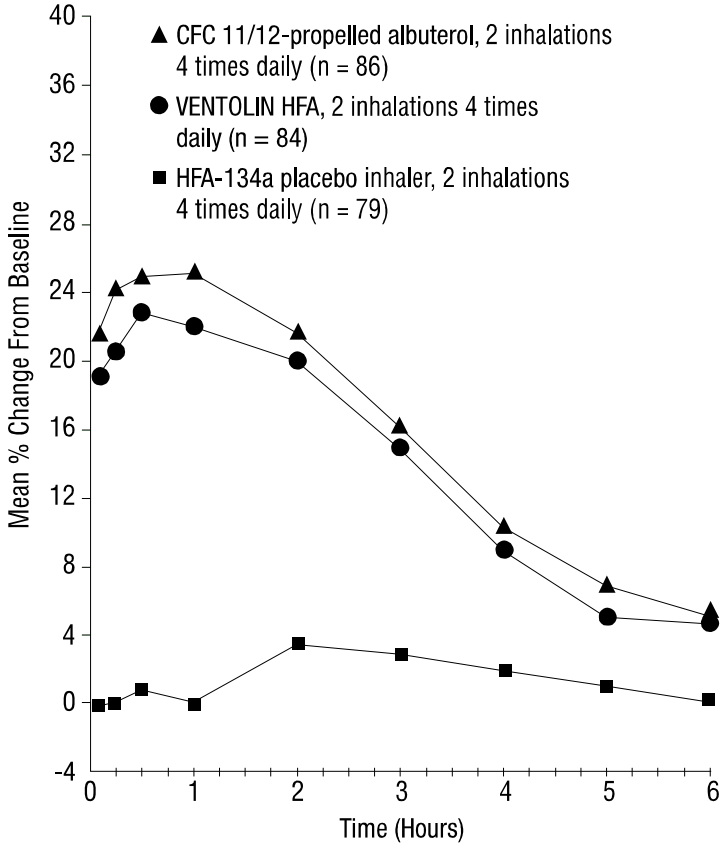
CLINICAL TRIALS

In a 12-week, randomized, double-blind study, VENTOLIN HFA (101 patients) was compared to CFC 11/12-propelled albuterol (99 patients) and an HFA-134a placebo inhaler (97 patients) in adolescent and adult patients 12 to 76 years of age with mild to moderate asthma. Serial forced expiratory volume in 1 second (FEV_1) measurements [shown below as percent change from test-day baseline at Day 1 (n = 297) and at Week 12 (n = 249)] demonstrated that 2 inhalations of VENTOLIN HFA produced significantly greater improvement in FEV_1 over the pretreatment value than placebo. Patients taking the HFA-134a placebo inhaler also took VENTOLIN HFA for asthma symptom relief on an as-needed basis.

FEV_1 as Percent Change From Predose in a Large, 12-Week Clinical Trial



Week 12



In the responder population (≥15% increase in FEV_1 within 30 minutes postdose) treated with VENTOLIN HFA, the mean time to onset of a 15% increase in FEV_1 over the pretreatment value was 5.4 minutes, and the mean time to peak effect was 56 minutes. The mean duration of effect as measured by a 15% increase in FEV_1 over the pretreatment value was approximately 4 hours. In some patients, duration of effect was as long as 6 hours.

A second 12-week randomized, double-blind study was conducted to evaluate the efficacy and safety of switching patients from CFC 11/12-propelled albuterol to VENTOLIN HFA. During the 3-week run-in phase of the study, all patients received CFC 11/12-propelled albuterol. During the double-blind treatment phase, VENTOLIN HFA (91 patients) was compared to CFC 11/12-propelled albuterol (100 patients) and an HFA-134a placebo inhaler (95 patients) in adolescent and adult patients with mild to moderate asthma. Serial FEV_1 measurements demonstrated that 2 inhalations of VENTOLIN HFA produced significantly greater improvement in pulmonary function than placebo. The switching from CFC 11/12-propelled albuterol inhaler to VENTOLIN HFA did not reveal any clinically significant changes in the efficacy profile.

In the 2 adult studies, the efficacy results from VENTOLIN HFA were significantly greater than placebo and were clinically comparable to those achieved with CFC 11/12-propelled albuterol, although small numerical differences in mean FEV_1 response and other measures were

observed. Physicians should recognize that individual responses to beta-adrenergic agonists administered via different propellants may vary and that equivalent responses in individual patients should not be assumed.

In a 2-week, randomized, double-blind study, VENTOLIN HFA was compared to CFC 11/12-propelled albuterol and an HFA-134a placebo inhaler in 135 pediatric patients (4 to 11 years old) with mild to moderate asthma. Serial pulmonary function measurements demonstrated that two inhalations of VENTOLIN HFA produced significantly greater improvement in pulmonary function than placebo and that there were no significant differences between the groups treated with VENTOLIN HFA and CFC 11/12-propelled albuterol. In the responder population treated with VENTOLIN HFA, the mean time to onset of a 15% increase in peak expiratory flow rate (PEFR) over the pretreatment value was 7.8 minutes, and the mean time to peak effect was approximately 90 minutes. The mean duration of effect as measured by a 15% increase in PEFR over the pretreatment value was greater than 3 hours. In some patients, duration of effect was as long as 6 hours.

One controlled clinical study in adult patients with asthma (N = 24) demonstrated that 2 inhalations of VENTOLIN HFA taken approximately 30 minutes prior to exercise significantly prevented exercise-induced bronchospasm (as measured by maximum percentage fall in FEV_1 following exercise) compared to an HFA-134a placebo inhaler. In addition, VENTOLIN HFA was shown to be clinically comparable to a CFC 11/12-propelled albuterol inhaler for this indication.

Some patients who participated in these clinical trials were using concomitant steroid therapy.

INDICATIONS AND USAGE

VENTOLIN HFA is indicated for the treatment or prevention of bronchospasm in adults and children 4 years of age and older with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm in patients 4 years of age and older.

CONTRAINDICATIONS

VENTOLIN HFA is contraindicated in patients with a history of hypersensitivity to albuterol or any other components of VENTOLIN HFA.

WARNINGS

Paradoxical Bronchospasm: Inhaled albuterol sulfate can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs, VENTOLIN HFA should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister.

Cardiovascular Effects: VENTOLIN HFA, like all other beta-adrenergic agonists, can produce clinically significant cardiovascular effects in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of VENTOLIN HFA at recommended doses, if they occur, the drug may need to be discontinued. In

addition, beta-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, VENTOLIN HFA, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Deterioration of Asthma: Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of VENTOLIN HFA than usual, this may be a marker of destabilization of asthma and requires reevaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids.

Use of Anti-Inflammatory Agents: The use of beta-adrenergic agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, e.g., corticosteroids, to the therapeutic regimen.

Immediate Hypersensitivity Reactions: Immediate hypersensitivity reactions may occur after administration of albuterol sulfate inhalation aerosol, as demonstrated by cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema.

Do Not Exceed Recommended Dose: Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

PRECAUTIONS

General: Albuterol sulfate, as with all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, hypertension, and cardiac arrhythmia; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and diastolic blood pressure have been seen in individual patients and could be expected to occur in some patients after use of any beta-adrenergic bronchodilator.

Large doses of intravenous albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. As with other beta-agonists, albuterol may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

Information for Patients: Patients being treated with VENTOLIN HFA should receive the following information and instructions. This information is intended to aid them in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

1. The action of VENTOLIN HFA should last up to 4 to 6 hours. VENTOLIN HFA should not be used more frequently than recommended. Do not increase the dose or frequency of doses of VENTOLIN HFA without consulting the physician. If patients find that treatment with

VENTOLIN HFA becomes less effective for symptomatic relief, symptoms become worse, and/or they need to use the product more frequently than usual, they should seek medical attention immediately. While patients are using VENTOLIN HFA, other inhaled drugs and asthma medications should be taken only as directed by the physician.

2. Common adverse effects of treatment with inhaled albuterol include palpitations, chest pain, rapid heart rate, tremor, and nervousness.
3. Patients who are pregnant or nursing should contact their physicians about the use of VENTOLIN HFA.
4 In general, the technique for administering VENTOLIN HFA to children is similar to that for adults. Children should use VENTOLIN HFA under adult supervision, as instructed by the patient's physician. (See Patient's Instructions for Use leaflet accompanying the product.)
5. Priming VENTOLIN HFA is essential to ensure appropriate albuterol content in each actuation. To prime the inhaler, release 4 test sprays into the air away from the face, shaking well before each spray. The inhaler should be primed before using it for the first time, when it has not been used for more than 2 weeks, or when it has been dropped.
6. KEEPING THE PLASTIC ACTUATOR CLEAN IS VERY IMPORTANT TO PREVENT MEDICATION BUILD-UP AND BLOCKAGE. THE ACTUATOR SHOULD BE WASHED, SHAKEN TO REMOVE EXCESS WATER, AND AIR-DRIED THOROUGHLY AT LEAST ONCE A WEEK. THE INHALER MAY CEASE TO DELIVER MEDICATION IF NOT PROPERLY CLEANED.

   The actuator should be cleaned (with the canister removed) by running warm water through the top and bottom for 30 seconds at least once a week. Do not attempt to clean the metal canister, including the counter, or allow the metal canister to become wet. Never immerse the metal canister in water. Shake the actuator to remove excess water, then air-dry thoroughly (such as overnight). When the actuator is dry, shake the canister well, then immediately insert the canister fully and firmly into the actuator and spray once into the air away from the face. Replace the mouthpiece cap.

   If it is necessary to use the inhaler before it is completely dry, shake excess water off the actuator. Shake the canister well, then immediately insert the canister fully and firmly into the actuator and spray once into the air away from the face. Then take the prescribed dose. After such use, the actuator should be rewashed and air-dried thoroughly.

   Blockage from medication build-up is more likely to occur if the actuator is not allowed to air-dry thoroughly. If the actuator should become blocked (little or no medication coming out of the mouthpiece) and the counter is not showing 000, the blockage may be removed by washing the actuator as described above.
7. Use VENTOLIN HFA only with the actuator supplied with the product. Discard the inhaler when the counter reads 000 (after 200 sprays have been used) or 3 months after removal from the moisture-protective foil pouch, whichever comes first. When the counter reads 020, contact the pharmacist for a refill of medication or consult the physician to determine whether a prescription refill is needed. Never try to alter the numbers or remove the counter from the

metal canister. Never immerse the canister in water to determine the amount of drug remaining in the canister.

8. For the proper use of VENTOLIN HFA, the patient should read and carefully follow the Patient's Instructions for Use leaflet accompanying the product.

Drug Interactions: Other short-acting sympathomimetic aerosol bronchodilators should not be used concomitantly with albuterol. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

Monoamine Oxidase Inhibitors or Tricyclic Antidepressants: VENTOLIN HFA should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of albuterol on the vascular system may be potentiated.

Beta-Blockers: Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta-agonists, such as VENTOLIN HFA, but may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers should be considered, although they should be administered with caution.

Diuretics: The ECG changes and/or hypokalemia that may result from the administration of nonpotassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with nonpotassium-sparing diuretics.

Digoxin: Mean decreases of 16% to 22% in serum digoxin levels were demonstrated after single-dose intravenous and oral administration of albuterol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical significance of these findings for patients with obstructive airway disease who are receiving albuterol and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and albuterol.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2-year study in Sprague-Dawley rats, albuterol sulfate caused a dose-related increase in the incidence of benign leiomyomas of the mesovarium at and above dietary doses of 2.0 mg/kg (approximately 14 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 6 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). In another study this effect was blocked by the coadministration of propranolol, a non-selective beta-adrenergic antagonist. In an 18-month study in CD-1 mice, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 500 mg/kg (approximately 1,700 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 800 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). In a 22-month study in Golden hamsters, albuterol sulfate showed no evidence of

tumorigenicity at dietary doses of up to 50 mg/kg (approximately 225 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 110 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis).

Albuterol sulfate was not mutagenic in the Ames test or a mutation test in yeast. Albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or in an AH1 strain mouse micronucleus assay.

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses of albuterol sulfate up to 50 mg/kg (approximately 340 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Albuterol sulfate has been shown to be teratogenic in mice. A study in CD-1 mice given albuterol sulfate subcutaneously showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg (less than the maximum recommended daily inhalation dose for adults on a mg/m^2 basis) and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg (approximately 8 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). The drug did not induce cleft palate formation at a dose of 0.025 mg/kg (less than the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated subcutaneously with 2.5 mg/kg of isoproterenol (positive control).

A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 fetuses (37%) when albuterol sulfate was administered orally at a 50 mg/kg dose (approximately 680 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

In an inhalation reproduction study in New Zealand white rabbits, albuterol sulfate/HFA-134a formulation exhibited enlargement of the frontal portion of the fetal fontanelles at and above inhalation doses of 0.0193 mg/kg (less than the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

A study in which pregnant rats were dosed with radiolabeled albuterol sulfate demonstrated that drug-related material is transferred from the maternal circulation to the fetus.

There are no adequate and well-controlled studies of VENTOLIN HFA or albuterol sulfate in pregnant women. VENTOLIN HFA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

During worldwide marketing experience, various congenital anomalies, including cleft palate and limb defects, have been reported in the offspring of patients being treated with albuterol. Some of the mothers were taking multiple medications during their pregnancies. No consistent pattern of defects can be discerned, and a relationship between albuterol use and congenital anomalies has not been established.

Use in Labor and Delivery: Because of the potential for beta-agonist interference with uterine contractility, use of VENTOLIN HFA for relief of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk.

Tocolysis: Albuterol has not been approved for the management of preterm labor. The benefit:risk ratio when albuterol is administered for tocolysis has not been established. Serious

adverse reactions, including maternal pulmonary edema, have been reported during or following treatment of premature labor with $beta_2$-agonists, including albuterol.

Nursing Mothers: Plasma levels of albuterol sulfate and HFA-134a after inhaled therapeutic doses are very low in humans, but it is not known whether the components of VENTOLIN HFA are excreted in human milk. Because of the potential for tumorigenicity shown for albuterol in animal studies and lack of experience with the use of VENTOLIN HFA by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Caution should be exercised when albuterol sulfate is administered to a nursing woman.

Pediatric Use: Results from a 2-week, randomized study in pediatric patients 4 to 11 years old with mild to moderate asthma have shown that VENTOLIN HFA is safe and effective in this population. Safety and effectiveness in children below 4 years of age have not been established.

Geriatric Use: Clinical studies of VENTOLIN HFA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Adverse reaction information concerning VENTOLIN HFA is derived from two 12-week, randomized, double-blind studies in 610 adolescent and adult patients with asthma that compared VENTOLIN HFA, a CFC 11/12-propelled albuterol inhaler, and an HFA-134a placebo inhaler. The following table lists the incidence of all adverse events (whether considered by the investigator to be related or unrelated to drug) from these studies that occurred at a rate of 3% or greater in the group treated with VENTOLIN HFA and more frequently in the group treated with VENTOLIN HFA than in the HFA-134a placebo inhaler group. Overall, the incidence and nature of the adverse events reported for VENTOLIN HFA and a CFC 11/12-propelled albuterol inhaler were comparable. Results in a 2-week pediatric clinical study (N = 135) showed that the adverse event profile was generally similar to that of the adult.

Overall Adverse Events With ≥3% Incidence in 2 Large 12-Week Clinical Trials in Adolescents and Adults*

Adverse Event	Percent of Patients		
	VENTOLIN HFA (n = 202) %	CFC 11/12-Propelled Albuterol Inhaler (n = 207) %	Placebo HFA-134a (n = 201) %
Ear, nose, and throat			
Throat irritation	10	6	7
Upper respiratory inflammation	5	5	2
Lower respiratory			
Viral respiratory infections	7	4	4
Cough	5	2	2
Musculoskeletal			
Musculoskeletal pain	5	5	4

*This table includes all adverse events (whether considered by the investigator to be drug-related or unrelated to drug) that occurred at an incidence rate of at least 3.0% in the group treated with VENTOLIN HFA and more frequently in the group treated with VENTOLIN HFA than in the HFA-134a placebo inhaler group.

Adverse events reported by less than 3% of the adolescent and adult patients receiving VENTOLIN HFA and by a greater proportion of patients receiving VENTOLIN HFA than receiving HFA-134a placebo inhaler and that have the potential to be related to VENTOLIN HFA include diarrhea, laryngitis, oropharyngeal edema, cough, lung disorders, tachycardia, and extrasystoles. Palpitation and dizziness have also been observed with VENTOLIN HFA.

Cases of urticaria, angioedema, rash, bronchospasm, hoarseness, and arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles) have been reported after the use of albuterol, USP.

In addition, albuterol, like other sympathomimetic agents, can cause adverse reactions such as hypertension, angina, vertigo, central nervous system stimulation, sleeplessness, headache, and drying or irritation of the oropharynx.

OVERDOSAGE

The expected symptoms with overdosage are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and sleeplessness. Hypokalemia may also occur.

As with all sympathomimetic aerosol medications, cardiac arrest and even death may be associated with abuse of VENTOLIN HFA. Treatment consists of discontinuation of VENTOLIN HFA together with appropriate symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of VENTOLIN HFA.

The oral median lethal dose of albuterol sulfate in mice is greater than 2,000 mg/kg (approximately 6,800 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 3,200 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). In mature rats, the subcutaneous median lethal dose of albuterol sulfate is approximately 450 mg/kg (approximately 3,000 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 1,400 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). In young rats, the subcutaneous median lethal dose is approximately 2,000 mg/kg (approximately 14,000 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 6,400 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). The inhalation median lethal dose has not been determined in animals.

DOSAGE AND ADMINISTRATION

Adult and Pediatric Asthma: For treatment of acute episodes of bronchospasm or prevention of asthmatic symptoms, the usual dosage for adults and children 4 years of age and older is 2 inhalations repeated every 4 to 6 hours; in some patients, 1 inhalation every 4 hours may be sufficient. More frequent administration or a larger number of inhalations is not recommended.

Priming VENTOLIN HFA is essential to ensure appropriate albuterol content in each actuation. To prime the inhaler, release 4 test sprays into the air away from the face, shaking well before each spray. The inhaler should be primed before using it for the first time, when the inhaler has not been used for more than 2 weeks, or when it has been dropped.

VENTOLIN HFA can also be used to relieve acute symptoms of asthma. The use of VENTOLIN HFA can be continued as medically indicated to control recurring bouts of bronchospasm. If a previously effective dosage regimen fails to provide the usual response, this may be a marker of destabilization of asthma and requires reevaluation of the patient and the treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids.

Safe usage of albuterol for periods extending over several years has been documented.

Exercise-Induced Bronchospasm Prevention: The usual dosage for adults and children 4 years and older is 2 inhalations 15 to 30 minutes before exercise. For treatment, see above.

Cleaning: To maintain proper use of this product, it is important that the actuator be washed and dried thoroughly at least once a week. The inhaler may cease to deliver medication if not properly cleaned and dried thoroughly. **See PRECAUTIONS: Information for Patients**.

Keeping the plastic actuator clean is very important to prevent medication build-up and blockage. If the actuator becomes blocked with drug, washing the actuator will remove the blockage.

HOW SUPPLIED

VENTOLIN HFA (albuterol sulfate HFA inhalation aerosol) is supplied as a pressurized aluminum canister fitted with a counter with a blue plastic actuator and a blue strapcap packaged within a moisture-protective foil pouch, each in boxes of 1 with patient's instructions (NDC 0173-0682-20). The moisture-protective foil pouch also contains a desiccant that should be discarded when the pouch is opened.

Priming VENTOLIN HFA is essential to ensure appropriate albuterol content in each actuation. To prime the inhaler, release 4 test sprays into the air away from the face, shaking well before each spray. The inhaler should be primed before using it for the first time, when the inhaler has not been used for more than 2 weeks, or when it has been dropped.

After priming, each actuation delivers 120 mcg of albuterol sulfate, USP in 75 mg of suspension from the valve and 108 mcg of albuterol sulfate, USP from the mouthpiece (equivalent to 90 mcg of albuterol base from the mouthpiece). The canister is labeled with a net weight of 18 g and contains 200 metered inhalations.

The blue actuator supplied with VENTOLIN HFA should not be used with any other product canisters, and actuators from other products should not be used with a VENTOLIN HFA canister.

The correct amount of medication in each inhalation cannot be assured after the counter reads 000, even though the canister is not completely empty and will continue to operate. The inhaler should be discarded when the counter reads 000 (after 200 actuations have been used) or 3 months after removal from the moisture-protective foil pouch, whichever comes first. Never immerse the canister in water to determine the amount of drug remaining in the canister.

Keep out of reach of children. Avoid spraying in eyes.

Contents Under Pressure: Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw container into fire or incinerator.

Store between 15° and 25°C (59° and 77°F). Store the inhaler with the mouthpiece down. For best results, the inhaler should be at room temperature before use. SHAKE WELL BEFORE USING.

VENTOLIN HFA does not contain chlorofluorocarbons (CFCs) as the propellant.

GlaxoSmithKline
Research Triangle Park, NC 27709

Month Year RL-

PATIENT'S INSTRUCTIONS FOR USE

VENTOLIN® HFA
(albuterol sulfate HFA inhalation aerosol)

Read this leaflet carefully before using your VENTOLIN HFA.

About VENTOLIN HFA

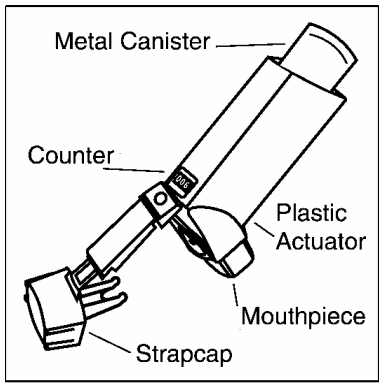


Figure 1

Your doctor has prescribed VENTOLIN HFA Inhalation Aerosol. VENTOLIN HFA is a bronchodilator.

The blue actuator supplied with VENTOLIN HFA should not be used with any other product canisters, and actuators from other products should not be used with a VENTOLIN HFA canister.

The metal canister is fitted with a counter to show the number of sprays of medicine you have left. The number will show through a window in the back of the plastic actuator (see Figure 1).

The counter starts at 204 (which includes the first 4 priming sprays) and counts down to 000. Each time you release a spray from the inhaler, the number will count down by 1. The counter will stop counting at 000.

Never try to alter the numbers or detach the counter from the metal canister. The counter cannot be reset and is permanently attached to the canister.

Priming Your VENTOLIN HFA

Priming VENTOLIN HFA as directed is important to ensure that you receive the appropriate amount of medicine. VENTOLIN HFA should be primed at certain times as described below.

VENTOLIN HFA should be primed before using it for the first time. Remove your VENTOLIN HFA from the overwrap and safely discard the overwrap and drying packet, which is also inside the overwrap. The counter should read 204.

To prime the inhaler, remove the cap from the mouthpiece of the actuator (the strap on the cap will stay attached to the actuator), shake the inhaler well, then spray 4 times into the air away from your face, shaking well before each spray. After you have primed the inhaler the first time, the counter will read 200.

VENTOLIN HFA should also be primed when the inhaler has not been used for more than 14 days or when the inhaler has been dropped. To prime the inhaler, remove the cap from the mouthpiece of the actuator (the strap on the cap will stay attached to the actuator), shake the inhaler well, then spray 4 times into the air away from your face, shaking well before each spray. When you prime the inhaler during regular use, the counter number will count down by 1 each time you spray the inhaler.

How to Use Your VENTOLIN HFA

Children 4 years of age and older should use VENTOLIN HFA under adult supervision, as instructed by the patient's doctor.

The inhaler should be at room temperature before use. Make sure that the canister is seated in the plastic actuator before each use.

Your VENTOLIN HFA should be primed before using it for the first time. VENTOLIN HFA should also be primed when the inhaler has not been used for more than 14 days or when the inhaler has been dropped. Make sure to read and follow the above instructions for Priming Your VENTOLIN HFA.

SHAKE THE INHALER WELL immediately before each spray.

Follow the instructions below. If you have any questions, ask your doctor or pharmacist.

1. **REMOVE THE CAP FROM THE MOUTHPIECE OF THE ACTUATOR (see Figure 2)**; the strap on the cap will stay attached to the actuator. Inspect the inhaler mouthpiece for the presence of foreign objects before each use, especially if the strap is no longer attached to the actuator or if the cap is not being used to cover the mouthpiece. Make sure the canister is fully and firmly inserted into the actuator. **SHAKE THE INHALER WELL** immediately before each spray.

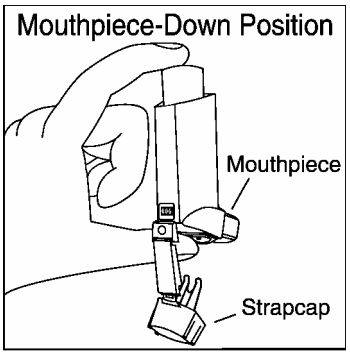


Figure 2

2. **BREATHE OUT FULLY THROUGH YOUR MOUTH,** expelling as much air from your lungs as possible. Place the mouthpiece fully into your mouth, holding the inhaler with the mouthpiece down (see Figure 2) and closing your lips around it.

3. **WHILE BREATHING IN DEEPLY AND SLOWLY THROUGH YOUR MOUTH, FULLY DEPRESS THE TOP OF THE METAL CANISTER** with your index finger (see Figure 3). Immediately after the spray is delivered, release your finger from the canister. When you have breathed in fully, remove the inhaler from your mouth and close your mouth.

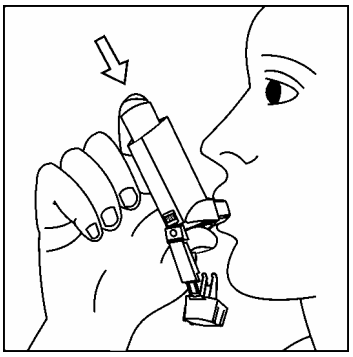


Figure 3

4. **HOLD YOUR BREATH AS LONG AS POSSIBLE**, up to 10 seconds, then breathe normally.

5. If your doctor has prescribed additional sprays, wait 1 minute and **SHAKE** the inhaler again. Repeat steps 2 through 4.

6. **REPLACE THE CAP ON THE MOUTHPIECE AFTER EACH USE.**

7. Because of the difference in propellants, you may notice a slightly different taste or feel of the spray in your mouth with VENTOLIN HFA than you are used to with other albuterol inhalation aerosol products.

8. Never immerse the canister in water to determine the amount of drug left in the canister ("float test").

9. **DISCARD THE INHALER WHEN THE COUNTER READS 000 (after you have used 200 inhalations) or 3 months after removal from the moisture-protective foil pouch, whichever comes first.** The correct amount of medicine in each inhalation cannot be assured after the counter reads 000, even though the canister is not completely empty and will continue to operate. When the counter reads 020, you should contact your pharmacist for a refill of your prescription or consult your doctor to determine whether a refill of your prescription is needed. Just as you should not take extra doses without consulting your doctor, you also should not stop using VENTOLIN HFA without consulting your doctor.

DO NOT use after the expiration date, shown as "EXP", on the product label and box.

Cleaning Your VENTOLIN HFA

KEEPING THE PLASTIC ACTUATOR CLEAN IS VERY IMPORTANT TO PREVENT MEDICINE BUILD-UP AND BLOCKAGE. THE ACTUATOR SHOULD BE WASHED, SHAKEN TO REMOVE EXCESS WATER, AND AIR-DRIED THOROUGHLY AT LEAST ONCE A WEEK. THE INHALER MAY STOP SPRAYING IF NOT PROPERLY CLEANED.

Routine cleaning instructions:

Step 1. Remove the canister from the actuator, and remove the cap from the mouthpiece of the actuator. The strap on the cap will stay attached to the actuator.

Step 2. Wash the actuator through the top and bottom with warm running water for 30 seconds at least once a week (see Figure 4). **Do not try to clean the metal canister**, including the counter, **or allow the metal canister to become wet.**

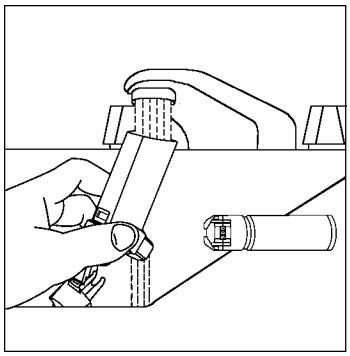


Figure 4

Step 3. To dry, shake off excess water and let the actuator air-dry thoroughly, such as overnight (see Figure 5).

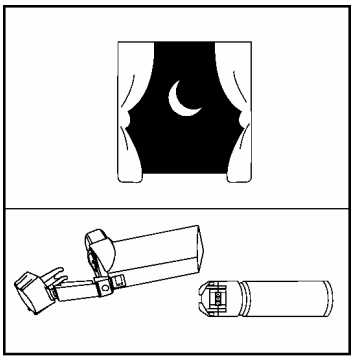


Figure 5

Step 4. When the actuator is dry, shake the canister well, then immediately insert the canister fully and firmly into the actuator (as shown in Figure 2) and spray once into the air away from your face. (The counter will count down by 1.) Replace the mouthpiece cap.

Blockage from medicine build-up is more likely to occur if the actuator is not allowed to air-dry thoroughly. **IF THE ACTUATOR BECOMES BLOCKED** (little or no medicine coming out of the mouthpiece and the counter is not showing 000, see Figure 6), wash the actuator as described in Step 2 and air-dry thoroughly as described in Step 3.

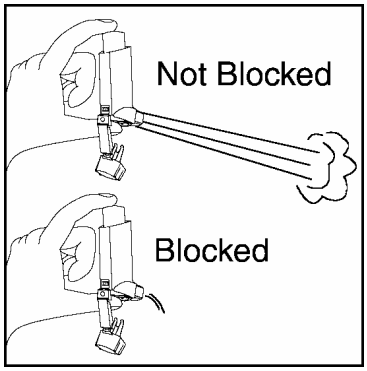


Figure 6

IF YOU NEED TO USE YOUR INHALER BEFORE THE ACTUATOR IS COMPLETELY DRY, SHAKE EXCESS WATER off the actuator. Shake the canister well, immediately insert the canister fully and firmly into the actuator (as shown in Figure 2), and spray once into the air away from your face. Then take your dose as prescribed. **After such use, rewash and air-dry thoroughly as described in Steps 2 and 3.**

Storing Your VENTOLIN HFA

Store at room temperature with the mouthpiece down. Keep out of reach of children.

Contents Under Pressure: Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw into fire or incinerator.

Further Information

DOSAGE: Use only as directed by your doctor.

WARNINGS: The action of VENTOLIN HFA should last up to 4 to 6 hours. VENTOLIN HFA should not be used more frequently than recommended. Do not increase the dose or frequency of VENTOLIN HFA without consulting your doctor. If you find that treatment with VENTOLIN HFA becomes less effective for symptomatic relief, your symptoms become worse, and/or you need to use the product more frequently than usual, you should seek medical attention immediately. While you are using VENTOLIN HFA, other inhaled drugs and asthma medicines should be used only as directed by your doctor. If you are pregnant or nursing, contact your doctor about the use of VENTOLIN HFA.

Adverse effects of treatment with VENTOLIN HFA include palpitations, chest pain, rapid heart rate, tremor, or nervousness. Effective and safe use of VENTOLIN HFA includes an understanding of the way that it should be administered. Use VENTOLIN HFA only with the actuator supplied with the product. The VENTOLIN HFA actuator should not be used with other aerosol medicines.

REMEMBER: This medicine has been prescribed for you by your doctor. DO NOT give this medicine to anyone else.

Please note that the CFC symbol on each product box means that VENTOLIN HFA does not contain chlorofluorocarbons (CFCs) as the propellant. Instead, the inhaler contains a hydrofluoroalkane (HFA-134a) as the propellant.

This leaflet does not contain the complete information about your medicine. *If you have any questions, or are not sure about something, then you should ask your doctor or pharmacist.*

You may want to read this leaflet again. Please DO NOT THROW IT AWAY until you have finished your medicine.

GlaxoSmithKline
Research Triangle Park, NC 27709

Month Year RL-

The blue actuator supplied with VENTOLIN® HFA (albuterol sulfate HFA inhalation aerosol) should not be used with any other product canisters, and actuators from other products should not be used with a VENTOLIN HFA canister.

The metal canister is fitted with a counter to show the number of sprays of medicine you have left. The number will show through a window in the back of the plastic actuator (see Figure 1). The counter starts at 204 and the number will count down by 1 each time you release a spray from the inhaler.

Never try to alter the numbers or detach the counter from the metal canister. The counter cannot be reset and is permanently attached to the canister.

Priming VENTOLIN HFA as directed is important to ensure you receive the appropriate amount of medicine. To prime the inhaler, remove the cap from the mouthpiece of the actuator (see Figure 1), then spray 4 times into the air away from your face, shaking well before each spray. You should prime the inhaler before using it for the first time, when it has not been used for more than 14 days, or when it has been dropped.

SHAKE THE INHALER WELL immediately before each spray.

1. REMOVE THE CAP FROM THE MOUTHPIECE of the actuator (see Figure 1); the strap on the cap will stay attached to the actuator. Inspect the inhaler mouthpiece for the presence of foreign objects before each use, especially if the strap is no longer attached to the actuator or if the cap is not being used to cover the mouthpiece. Make sure the canister is fully and firmly inserted into the actuator.

2. BREATHE OUT FULLY THROUGH YOUR MOUTH, expelling as much air from your lungs as possible. Place the mouthpiece fully into your mouth, holding the inhaler with the mouthpiece down (see Figure 1) and closing your lips around it.

3. WHILE BREATHING IN DEEPLY AND SLOWLY THROUGH YOUR MOUTH, FULLY DEPRESS THE TOP OF THE METAL CANISTER with your index finger (see Figure 2). Immediately after the spray is delivered, release your finger from the canister. When you have breathed in fully, remove the inhaler from your mouth and close your mouth.

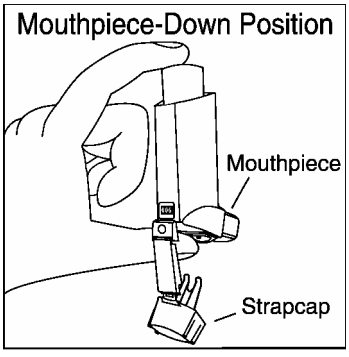


Figure 1

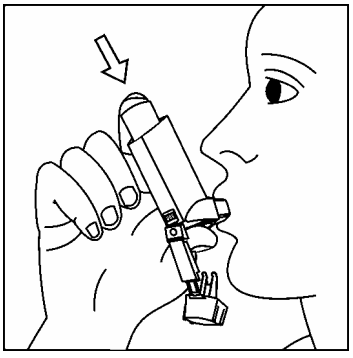


Figure 2

4. HOLD YOUR BREATH AS LONG AS POSSIBLE, up to 10 seconds, then breathe normally.

5. If your doctor has prescribed additional sprays, wait 1 minute and **SHAKE** the inhaler again. Repeat steps 2 through 4.

6. REPLACE THE CAP ON THE MOUTHPIECE AFTER EACH USE.

7. KEEPING THE PLASTIC ACTUATOR CLEAN IS VERY IMPORTANT TO PREVENT MEDICINE BUILD-UP AND BLOCKAGE. THE ACTUATOR SHOULD BE WASHED, SHAKEN TO REMOVE EXCESS WATER, AND AIR-DRIED THOROUGHLY AT LEAST ONCE A WEEK. THE INHALER MAY STOP SPRAYING IF NOT PROPERLY CLEANED.

See enclosed Patient's Instructions for Use for detailed cleaning instructions.

8. Because of the difference in propellants, you may notice a slightly different taste or feel of the spray in your mouth with VENTOLIN HFA than you are used to with other albuterol inhalation aerosol products.

9. Never immerse the canister in water to determine the amount of drug left in the canister ("float test").

10. DISCARD THE INHALER WHEN THE COUNTER READS 000 **(after you have used 200 inhalations) or 3 months after removal from the moisture-protective foil pouch, whichever comes first.** The correct amount of medicine in each inhalation cannot be assured after the counter reads 000, even though the canister is not completely empty and will continue to operate. When the counter reads 020, you should contact your pharmacist for a refill of your prescription or consult your doctor to determine whether a refill of your prescription is needed. Just as you should not take extra doses without consulting your doctor, you also should not stop using VENTOLIN HFA without consulting your doctor.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-983/S009

MEDICAL REVIEW(S)

DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS
MEDICAL OFFICER CONSULTATION

Date:	April 4, 2005
To:	Craig Bertha, Ph. D., HFD-570
From:	Sally Seymour, M.D., Medical Officer, DPADP, HFD-570
Through:	Eugene Sullivan, M.D., F.C.C.P., Deputy Division Director, DPADP
Through:	Badrul Chowdhury, M.D., Ph.D., Division Director, DPADP
Subject:	NDA# 20-983 Prior Approval, CMC, Supplement

NDA/IND#:	NDA# 20-983 Prior Approval, CMC, Supplement
Applicant:	GlaxoSmithKline
Drug Product:	Ventolin HFA
Protocol:	SB030003, SAS30033
Request From:	Craig Bertha, Ph. D., HFD-570
Date of Request:	January 10, 2005
Date Received:	January 10, 2005
Materials Reviewed:	EDR submission NDA# 20983, S-009, dated December 17, 2004

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1 INTRODUCTION

This is a Medical Officer consultation regarding a Prior Approval CMC Supplement for Ventolin HFA fitted with a dose counter. In this submission, GSK proposes albuterol sulfate HFA fitted with a dose counter. The primary support for this CMC supplement is in vitro data for Ventolin HFA with counter. However, the supplement also includes two patient handling studies and proposed labeling changes. The CMC reviewer, Dr. Craig Bertha, requested a clinical review of the two patient handling studies, safety data, and proposed labeling. The Executive Summary summarizes the findings of the consult while the remainder of this document provides background information, a detailed review of the clinical studies, and recommendations for labeling.

Table of Contents

2 EXECUTIVE SUMMARY

From a clinical perspective, the patient handling studies in this submission provide adequate clinical support for Approval of this supplement for albuterol sulfate HFA MDI with counter. The primary source of clinical data is Study SB030003, which was a patient handling study with albuterol sulfate HFA MDI with counter. Diary card data collected in Study SB030003 suggest an acceptable level of clinical performance of albuterol sulfate HFA MDI with counter. Study SAS30033 was a patient handling study with fluticasone proprionate/salmeterol HFA MDI with counter, which provides supportive clinical performance data because the dose counter in both products is the same.

The primary support for this supplement is in vitro data of albuterol sulfate HFA MDI with counter. The purpose of the patient handling studies is to supplement the in vitro data and provide information regarding any problems noted when the counter is used in a clinical setting. The patient handling studies were also designed to capture any discrepancies between the dose counter and patient diaries. In addition to discrepancies between the dose counter and patient diaries, the size of the discrepancy (or number of miscounts) was also determined. For instance, one discrepancy between the patient diary and dose counter may represent a difference of two actuations (or two miscounts). However, miscounts in the clinical studies based upon patient diary data are problematic as some of the types of miscounts recorded by subjects were mechanically impossible. In addition, a review of the diaries of subjects with large miscounts suggests many of the discrepancies were due to diary recording errors or data entry errors. Thus, the patient diary data likely overestimated the number of miscounts.

The patient handling studies in this supplement did not suggest any major problems with the counter in the clinical setting. Both studies demonstrated that the primary discrepancies between the patient diaries and the counter tended to be overcounting by the counter. Of the types of miscounts recorded, undercounting is of particular interest. Undercounting by the dose counter could lead to a patient using the inhaler past the labeled number of actuations, which is a safety issue. Both studies demonstrated that undercounting was quite low. Based on the patient diary data, over the course of the life of the MDI (200 actuations), undercounting occurred less than once. In addition to the number of actuations recorded in the patient diaries, the number of actuations was estimated based upon returned canister weights. Canister weights also suggested the dose counter tended to overcount, not undercount.

Optimization of the dose counter suggests that miscounts will be less than what was noted in the patient handling studies. GSK conducted the patient handling studies with a prototype dose counter. In vitro studies of albuterol sulfate HFA with prototype counter demonstrated that 1.27% of the samples tested had count failures. However, the Applicant has optimized the prototype counter to minimize count failures. In vitro studies of albuterol sulfate HFA with optimized counter demonstrated that 0.02% of the samples tested had count failures. Thus, the optimized dose counter decreased the frequency of count failures.

There are no standards as to what is an acceptable discrepancy rate between patient diaries and MDI dose counters. Although the patient diary data suggested the dose counter tended to overcount, the benefits of the dose counter outweigh the potential downside of discarding the product early. A primary benefit of the counter is having an indication of the number of actuations remaining, which could help patients avoid using the product beyond the labeled number of actuations.

An issue discovered during the review period by the CMC reviewer was the increase in albuterol content in the first few actuations if albuterol sulfate HFA MDI with counter has not been used for several months. This issue appears to be related to albuterol sulfate HFA and not related to the counter. Because the increase in albuterol content could be a safety issue in certain patients, the product label should contain appropriate language regarding priming the inhaler.

A review of the safety data in both patient handling studies did not suggest a new safety signal. AEs noted in Study SB030003 were consistent with the current Ventolin HFA product label, while AEs noted in Study SAS30033 were consistent with the Advair Diskus product label.

The Applicant's proposed label was reviewed. Labeling recommendations are included in Section 7.

3 BACKGROUND

3.1 Product Information

Ventolin HFA with counter is the same formulation and packaging as the approved Ventolin HFA except that a counter has been fitted to the filled canister by a collar. The initial counter reading is 204. The counter counts down each actuation and displays the number of actuations remaining. After the initial four priming actuations recommended in the product label, the counter reads 200, which represents the labeled number of actuations. The counter displays the number of actuations remaining and counts down to '000.' There is no lockout of the inhaler at '000' but the counter does not change once '000' is reached.

Ventolin HFA Inhalation Aerosol is a metered dose inhaler (MDI), which was approved for marketing in the United States on April 19, 2001, for the treatment or prevention of bronchospasm in adults and children 4 years of age and older with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm in patients 4 years of age and older.

The drug substance is albuterol sulfate, which is a beta$_2$-adrenergic receptor agonist. Ventolin HFA contains a microcrystalline suspension of albuterol sulfate in hydrofluoroalkane (HFA)-134a propellant. Ventolin HFA does not contain chlorofluorocarbons (CFCs).

Advair HFA Inhalation aerosol is a metered dose inhaler, which contains fluticasone proprionate and salmeterol. Advair HFA is not approved for marketing in the United States. GSK submitted

NDA# 21-254 for Advair HFA on December 20, 2000. An Approvable action was taken October 19, 2001, primarily because of CMC deficiencies. A complete response was submitted April 15, 2002, and an Approvable action was taken October 16, 2002, primarily for CMC deficiencies.

3.2 Presubmission Regulatory Activity

The following are pertinent regulatory meetings for the development of Ventolin HFA with Counter.

- August 24, 2001, meeting between GSK and DPADP
    - The Division stated the Applicant should determine the valve actuation force for each drug product with the counter attached.
    - "Count-non-fire" is preferred to "fire not count"
    - The number on the counter should include the appropriate number of priming actuations (e.g. 124 = 4 priming sprays and 120 actuations)
    - Perform drop testing of the product
    - Qualification of MDI counter based on in vitro comparability data and clinical study
    - Patient handling study would be required and would need to include:
        - Pediatric and geriatric patients
        - Patients with asthma and COPD
    - One patient handling study could be used to support all HFA products with MDI counter provided there were no changes to the counter, valve forces were not significantly different between products, and in vitro data demonstrated no significant differences in product performance
- September 13, 2002, meeting between GSK and DPADP
    - DPADP agreed with the proposed patient handling study design for Ventolin HFA and Advair HFA and proposed endpoints
        - Applicant needs to assure equal representation of asthma and COPD patients in the studies
        - Applicant needs to assure sufficient numbers of patients use Ventolin for full 200 actuations
            - A study using scheduled-use would be acceptable
    - Applicant should be aware that certain changes made to Advair HFA prior to approval may make the results of the dose-counter study irrelevant
    - Since Advair HFA is not indicated for COPD, the Advair HFA study should not be used for any claim or promotional activity
    - Canister weights should be collected for all patients
    - Applicant stated Ventolin and Advair valves are not the same. The distance to fire may vary, but the distance to count will be the same between the two. The counter-unit will be biased towards "count-not-fire."
- October 8, 2004, DPADP faxed responses to CMC questions and one clinical question from Applicant
    - The Applicant asked if it is acceptable to not conduct a patient handling study for Flovent HFA and instead rely on the data form the Ventolin HFA study

    - The Division agreed one study could be sufficient provided that:
        - There are no changes to the counter
        - The valve forces were not different between products
        - In vitro data demonstrated no difference in product performance
        - The Ventolin HFA with Counter PAS is approved
        - The patient handling studies are adequate (pediatric and geriatric patients; asthma and COPD patients)
- October 12, 2004, teleconference between DPADP and GSK
    - Discussion of October 8, 2004, response to question regarding the release testing being conducted before the addition of the counter
    - The Division suggested GSK perform whatever release testing it felt appropriate without the counter fixation as an in-process-control to justify addition of the dose counter to the full batch. If GSK chooses to do some testing as final before the counter is affixed, it must show that the fixation of the dose counter does not impact on the devices functional attributes.

3.3 Financial Disclosures

The Applicant provided financial disclosure for the clinical investigators, which demonstrated one investigator with financial ties to the Applicant. Dr. (b) (6) declared a significant equity interest in GSK of greater than $50,000. Dr (b) (6) enrolled (b) subjects into Study SB030003 and (b) (6) subjects into Study SAS30033[N020983\S_009\2004-12-17\other\financial.pdf, p 2].
Reviewer's Comment: The small number of subjects enrolled by investigators with financial ties to the Applicant is unlikely to affect the results of the submitted studies.

4 SIGNIFICANT FINDINGS FROM CMC REVIEW

In vitro studies were conducted on the prototype dose counter utilized in the patient handling studies. For 27 batches of albuterol sulfate HFA with prototype counter, 3370 samples were tested and there were 43 count failures (1.27%) out of the 3370 samples. The Applicant has since optimized the dose counter. In vitro studies were conducted with albuterol sulfate HFA with optimized counter. Out of 82 batches of albuterol sulfate HFA with commercial counters, 35,523 samples were tested and there were 8 count failures (0.02%) out of the 35,523 samples. Thus, the optimized commercial dose counter decreased the frequency of count failures.
Reviewer's Comment: The Division prefers that the clinical studies use the to be marketed product. However, according to the CMC reviewer, the optimizations made to the dose counter are not major changes to the device. The changes made should reduce the discrepancy/count failure rates.

A CMC issue noted during the review period was the increase in albuterol content in the first few actuations of MDIs not used for several months. Priming data for albuterol sulfate with counter was submitted, which indicates the first few actuations may have a higher albuterol content than the labeled 90mcg per actuation. The following table shows the mean albuterol content per

actuation in two batches of albuterol sulfate HFA with counter, which have been stored for 8 months. According to the CMC reviewer, this issue is related to albuterol sulfate HFA MDI and not the counter.

Table 1 Mean Albuterol Content per Actuation (mcg)

	Priming Actuation #1	Priming Actuation #2	Priming Actuation #3	Priming Actuation #4	Actuation #1
Batch 041034824	395	145	98	97	87
Batch 4ZP0300	268	347	140	100	91

Source: N020983\S_009\2005-2-23\Response to Comment #6, page 1-10.

Reviewer's Comment: According to the CMC reviewer, the increase in albuterol content is an albuterol sulfate HFA issue and not related to the attachment of the counter. The increase in albuterol content was noted in batches that had been stored for 8 months. It is unclear exactly when this increase in albuterol content in the first few sprays occurs. An increase in albuterol content was also noted if the inhaler had been used and dropped. The increased albuterol content raises safety concerns. Therefore, the product label should contain appropriate language regarding priming after storing and priming after dropping.

Because of the increase in albuterol content in the first few actuations, the Applicant submitted labeling which included a recommendation to prime the MDI with 4 actuations if the inhaler had been dropped. Currently, the product label recommends priming the inhaler prior to first use or when the inhaler has not been used for more than 2 weeks. The Applicant also submitted a safety assessment to address the potential safety concerns associated with the increased albuterol content if the MDI is not primed properly. The safety assessment is discussed in the next section.

5 SAFETY ASSESSMENT OF INCREASED ALBUTEROL CONTENT IN PRIMING ACTUATIONS

To address potential safety concerns associated with a higher albuterol content in the first two actuations of albuterol sulfate HFA if the inhaler is not properly primed, the Applicant submitted a brief safety assessment. The safety assessment included the following information:

- Literature references
    - Patients with severe asthma tolerating albuterol doses of 3.5mg via MDI with minimal adverse outcomes
    - Ten patients with asthma tolerating 800 mcg of albuterol with little effect on HR, QTc, potassium, or tremor
    - The effect of higher doses of albuterol in the setting of acute asthma exacerbations
        - 62 children 1-24 months 200 mcg albuterol Q 10 minutes for 5 doses
            - Tremor observed in one child
        - 30 children 1-4 years 600mcg albuterol Q20 minutes
            - Mean change HR 2.4 bpm, tremor increased

- Reference to studies in the Ventolin HFA NDA suggesting that 360mcg of albuterol demonstrated no cardiovascular or metabolic adverse events
- A summary of GSK's albuterol safety database for overdoses of albuterol HFA
    - Symptoms were pharmacologically predicted effects of beta agonists
        - Tachycardia and tremor most common
- Patients with severe hypoxia and hypokalemia may be at greater risk of cardiac rhythm disturbances with higher doses of albuterol

The safety assessment suggests that higher doses of albuterol may be tolerated. However, patients prone to cardiovascular arrhythmias may be at increased risk of adverse events. Because of the potential for increased adverse events with higher doses of albuterol, the product label should contain appropriate language regarding priming.

6 SUMMARY OF CLINICAL STUDIES

The Applicant conducted two patient handling studies to support this supplement. Table 2 displays the clinical studies conducted by the Applicant. The results of the studies are summarized in the following sections. A detailed review of each of the studies is located in the Appendices.

Table 2 Clinical Studies

Study #	Study Purpose	Subjects	Design	Treatment Groups
SBO30003	Counter performance and safety	268 subjects ≥ 4 yrs of age with asthma or COPD	Open label, single arm	Ventolin HFA with counter 90mcg
SAS30033	Counter performance and safety	237 subjects ≥ 12 yrs of age with asthma or COPD	Open label, single arm	Advair HFA with counter 250/50mcg

6.1 Study SB030003

Conduct

Study SB030003 was an open label patient handling study with Ventolin HFA with Counter (albuterol sulfate HFA MDI with Counter) in 268 subjects with asthma and COPD aged four years and older. Subjects were assigned to open-label treatment with albuterol sulfate HFA MDI with counter following a screening period. Subjects were instructed to take two actuations of albuterol sulfate HFA MDI with counter twice a day (morning and evening) and to record MDI use and dose counter reading in their diary before and after each dose (two actuations). Subjects were to use the albuterol sulfate HFA MDI with counter until the labeled number of actuations (200) were used. Subjects were seen in the clinic every one to two weeks. Diary cards were collected at each clinic visit and AEs were reviewed. The albuterol sulfate MDI with counter was returned to the Applicant at the end of the study.

Demographics

The majority of the subjects were caucasian. The mean age was 39 years, with an age range of 4 to 90 years. A little over half of the subjects had asthma (59%), while 41% of subjects had COPD. Approximately 30% of the subjects were less than 12 years of age and 20% of the subjects were ≥ 65 years of age.
Reviewer's Comment: The population adequately satisfies the Division's request for including an equal representation of subjects with asthma and COPD, as well as pediatric and geriatric subjects.

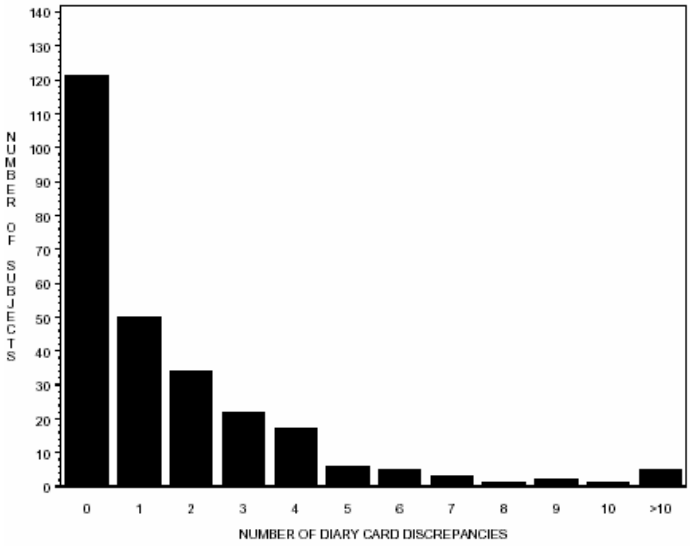
Populations
The majority of subjects (n=224) recorded at least 180 actuations on the diary card. This population was pre-specified as the primary population of interest by the Applicant and was defined as the completer population. The pertinent results for the completer population are included in Table 3 in this section and reviewed in detail in the Appendices, Section 7.1. The results for the ITT population (n=268) are reviewed here as this population included everyone assigned to albuterol sulfate HFA MDI with counter.
Reviewer's Comment: The Division requested that the subjects use the inhaler for the entire life of the inhaler.

Discrepancy Rates
The collected patient diary data was used to determine the number of discrepancies between the patient diaries and dose counter. In addition, for each discrepancy between the patient diary and dose counter, the size of the discrepancy (or number of miscounts) was determined. The size of the discrepancy is the actuation difference between the counter and patient diary. For example, the patient diary data may have one discrepancy with the dose counter, but the discrepancy size was four actuations.

Overall, there was a high level of concordance between the recorded actuations in patient diaries and the dose counter. Forty-five percent of subjects reported no discrepancy. Based upon diary recordings in the ITT population, 471 discrepancies were noted between diary recordings and the counter out of a total 48,721 reported actuations, which is a discrepancy rate of 0.0097 discrepancies per actuation. Based on 200 labeled actuations, the discrepancy rate for the ITT population was 1.93 discrepancies per 200 actuations.

As shown below in Figure 1, the majority of subjects who reported discrepancies, reported between one and four discrepancies. Overall, approximately 30% of subjects reported one to two discrepancies, while 2% of subjects (5 subjects) reported more than 10 discrepancies. The maximum number of discrepancies was 45.
Reviewer's Comment: The subject with 45 discrepancies was noted to have difficulty following diary card instruction and was discontinued from the study on day 28. The subject was noted to continue to take medication for 7 days after the counter reached zero, which contributed to some of the discrepancies [N020983\S_009\2004-12-17\clinstat\SB030003-02csr.pdf, p 1041].

Figure 1 Number of Diary Card Discrepancies per Subject (ITT Population)



Source: [N020983\S_009\2004-12-17\clinstat\SB030003-02csr.pdf, p 344]

Reviewer's Comment: Forty-five percent of subjects had no discrepancies between the diary card and counter.

The most common discrepancies were count not fire (CNF). For the ITT population, 209 CNF discrepancies were noted out of 48,721 subject reported actuations. Based on 200 labeled actuations in an MDI, the CNF discrepancy rate was 0.86 CNF discrepancies per 200 actuations for the ITT population.

Of particular interest are the fire not count (FNC) discrepancies. This type of discrepancy could lead to a patient using the MDI beyond the labeled number of actuations, which presents a safety concern. Out of 48,721 subject reported actuations, 50 FNC discrepancies were noted in the ITT population. Based on 200 labeled actuations, the FNC discrepancy rate per 200 actuations was 0.20.

Reviewer's Comment: There are no standards for discrepancy rates between patient diaries and MDI dose counters. The diary card recording is quite complex and could potentially overestimate the discrepancies. For example, some "count up unknown fire" discrepancies were noted. Counting up is mechanically impossible and most likely indicates diary card recording errors. That being said, the diary card data indicated that the FNC rate (undercounting) was low, which is important from a safety standpoint. The patient diaries indicated that the primary discrepancies tended to be overcounting (CNF). In general, the patient diaries indicate the discrepancy rate per 200 actuations in an MDI would be approximately 1.93 discrepancies per MDI. In this reviewer's opinion, the discrepancy rates in this study are acceptable.

Table 3 summarizes the key findings for Study SB030003 for the ITT and completer population. In general, the discrepancy rates and sizes were higher in the ITT population.

Table 3 Summary of Findings in Study SB030003

.	Completer (N=224)			ITT Population (N=268)		
	Number of discrepancies	Discrepancies per 200 actuations	Size of discrepancy per 200 actuations	Number of discrepancies	Discrepancies per 200 actuations	Size of discrepancy per 200 actuations
Total	333	1.52	4.09	471	1.93	5.78
Count Not Fire	173	0.79	1.02	209	0.86	1.13
Count Unknown Fire	103	0.47	1.81	184	0.76	2.77
Count Up Unknown Fire	19	0.09	0.97	28	0.12	1.53
Fire Not Count	38	0.17	0.30	50	0.20	0.34

Reviewer's Comment: The Applicant also determined the count up unknown fire (CUUF) discrepancies. Counting up is mechanically impossible. Thus, the CUUF discrepancies most likely were secondary to diary entry errors. Although the CUUF discrepancies were the lowest reported discrepancy, the size of the CUUF contributed 1.53 actuations to the overall discrepancy size.

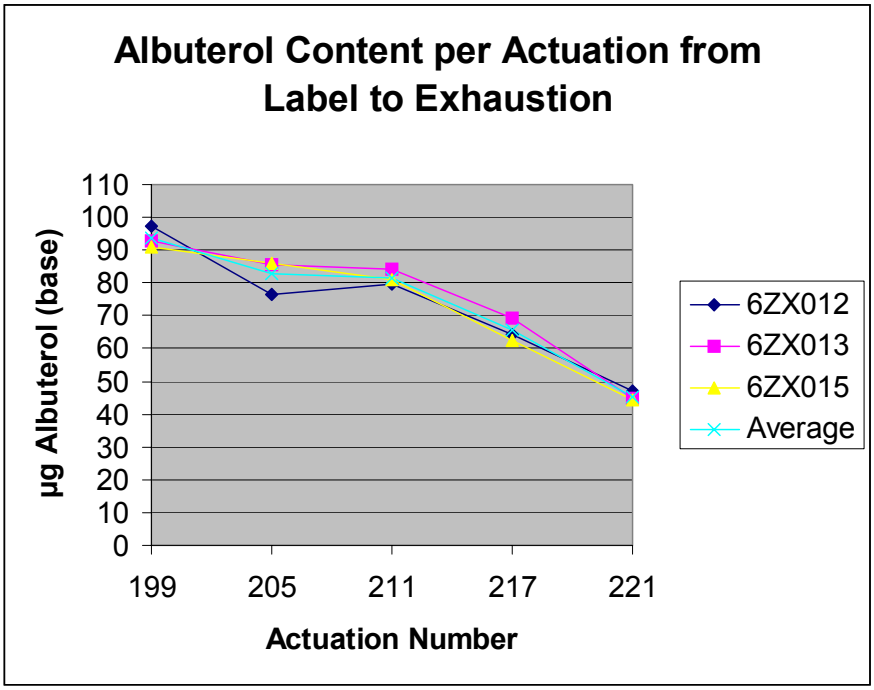
Discrepancy Size

As discussed above, for each discrepancy the number of actuations that were different between the counter and patient diary is called the size of the discrepancy. Most of the discrepancy sizes (or miscounts) were between one and two actuations. However ten subjects did report a discrepancy size of more than 5 actuations.

Reviewer's Comment: In the in vitro studies, when the counter failed, the majority of the failures were up to 2 counts. Two counters failed by 8 counts. The patient diaries of the subjects who had discrepancy size of more than 5 actuations were reviewed. Many of the discrepancies were due to data entry errors or diary card recording errors. Therefore, the discrepancy size (or miscounts) is likely overestimated by this patient handling study.

Undercounting (FNC) is of particular interest because of the potential for safety issues. As shown above in Table 3, less than one actuation (0.34 actuation) per 200 actuations was undercounted. Because of overfill of the MDI, one undercounted (FNC) actuation does not present a safety concern. Figure 2 displays the overfill for albuterol sulfate HFA MDI.

Figure 2 Albuterol Content per Actuation from Label to Exhaustion for Ventolin HFA



Source: Dr. Craig Bertha's CMC review of NDA# 20-983, dated October 14, 1998, page 27.

Reviewer's Comment: There is no lock out feature after the counter reaches '000.'

The above figure shows that the drop off of albuterol content past the labeled 200 actuations is gradual until approximately actuation 210, when the drop-off increases. Albuterol sulfate HFA with counter will start at 204 to prompt patients to prime the inhaler. Based on the above figure, the actuations between 204 to 210 have an albuterol content of 80mcg or more.
Reviewer's Comment: The overfill suggests that after the labeled 200 actuations, there are 5 to 10 additional actuations, which contain at least 80mcg of albuterol. The patient diary data suggests that less than one FNC (undercount) actuation occurred per 200 actuations. Based on the overfill data, an undercount of one actuation should not present a safety concern.

Weight Analysis
Returned canisters were evaluated for the number of actuations based upon weight. For the ITT population, based upon canister weight, the expected mean number of actuations was 174 with a range of 170-178 actuations. The mean number of actuations based upon diary recordings was 188 and captured by the counter was 190. Based upon the weight data, there appear to have been more overcounts (CNFs).
Reviewer's Comment: It is unclear to this reviewer which is more a more reliable determination of the actual actuations used, the weight data or the patient diary data. Both sources, however, suggest that the most common type of discrepancy is overcounting.

Investigation of Devices

Devices which had a "major failure" were investigated. Mechanical findings were noted in 6% of the devices. Some of the mechanical findings, including (b) (4), damaged (b) (4), damaged (b) (4), and (b) (4), may have contributed to FNC discrepancies.

Reviewer's Comment: "Major failure" was defined as the following

- *Any instance of Fire Not Count (FNC)*
- *Total diary card discrepancy size between recorded actuations and counter reading greater than the range tolerance (±8 actuations)*
- *Any situation as deemed necessary by the study team.*

Reviewer's Comment: According to the CMC reviewer, the Applicant has optimized some of the mechanical findings, which were noted in this study. Reportedly, the optimization will not produce significant differences in the device used in this study, but should improve the counting reliability of the device.

Patient Satisfaction

Patient satisfaction surveys indicated that over 90% of subjects reported satisfaction with the counter device and indicated the counter device would help them avoid running out of medication.

Safety

Overall, the incidence of AEs was 31%. Cough, pharyngolaryngeal pain, and headache were the most common AEs, which were consistent with the Ventolin HFA product label.

Reviewer's Comment: No new safety signals were raised in this study.

Conclusion

Study SB030003 provided clinical handling data with albuterol sulfate HFA with counter. There are no standards as to what is an acceptable discrepancy rate between patient diaries and MDI dose counters. The patient diary data may have overestimated discrepancies since some of the discrepancies recorded were mechanically impossible. Ideally, the dose counter should have a high level of accuracy and minimize any undercounting, as undercounting could lead to safety issues.

Study SB03003 did not suggest any major problem with the counter. There were discrepancies between the patient diary data and the counter. The majority of the discrepancies were overcounting. Undercounting was quite low. Over the course of the life of the MDI (200 actuations), undercounting occurred less than once.

Although the counter tended to overcount, the benefits of the dose counter outweigh the potential downside of discarding the device early. Benefits include having a reliable indicator of the number of actuations remaining. Not only will patients have a better idea when a refill is needed, but patients can avoid using the product beyond the labeled use.

In this reviewer's opinion, Study SB030003 demonstrates an acceptable level of accuracy of the dose counter based upon patient diaries. The diary card data provides clinical support to the in

vitro data. GSK conducted the patient handling studies with a prototype dose counter. In vitro studies demonstrated that 1.27% of the sampled products with the prototype counter had count failures. However, the Applicant has optimized the prototype to minimize count failures. In vitro studies demonstrated that 0.02% of sampled products with the optimized counter had count failures. Thus, the optimized dose counter decreased the frequency of count failures.

6.2 Study SAS30033

Conduct

Study SAS30033 was an open label patient handling study with fluticasone proprionate/salmeterol HFA MDI with counter in 237 subjects with asthma and COPD aged 12 years and older. Subjects were assigned to open-label treatment with fluticasone proprionate/salmeterol HFA MDI with counter following a screening period. Subjects were instructed to take two actuations of fluticasone proprionate/salmeterol HFA MDI with counter twice a day (morning and evening) and to record MDI use and dose counter reading in their diary before and after each dose (two actuations). Subjects were to use the fluticasone proprionate/salmeterol HFA MDI with counter until the maximum number of actuations (120) were used. Subjects were seen in the clinic every week. Diary cards were collected at each clinic visit and AEs were reviewed. The fluticasone proprionate/salmeterol HFA MDI with counter was returned to the Applicant at the end of the study.

Reviewer's Comment: Study SAS30033 provides supportive clinical data for albuterol sulfate HFA MDI because the dose counters are the same. Although the valves in the two products are different, the distance of travel needed to advance the counter is the same between the two products.

Demographics

The majority of the subjects were caucasian. The mean age was 54 years, with an age range of 14 to 86 years. A little over half of the subjects had asthma (54%), while 46% of subjects had COPD. Approximately one third of the subjects were ≥ 65 years of age.

Reviewer's Comment: The population adequately satisfies the Division's request for including an equal representation of subjects with asthma and COPD, as well as geriatric subjects.

Populations

The majority of subjects (n=228) recorded at least 108 actuations on the diary card. This population was pre-specified as the primary population of interest by the Applicant and was defined as the completer population. The pertinent results for the completer population are included in Table 5 in this section and reviewed in detail in the Appendices, Section 7.2. The results for the ITT population (n=237) are reviewed here as this population included everyone assigned to albuterol sulfate HFA MDI with counter.

Reviewer's Comment: In this study, the results for the ITT population and completer population are essentially the same.

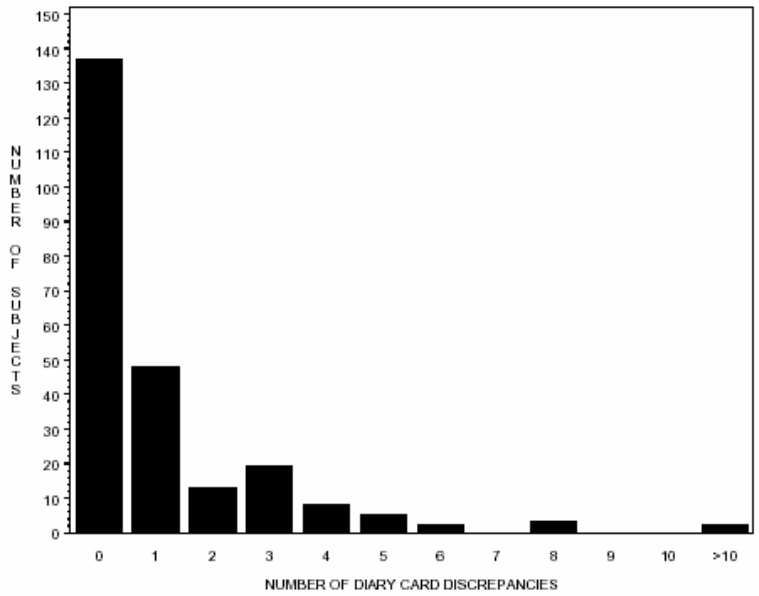
Discrepancy Rates

Overall, there was a high level of concordance between the recorded actuations in the diary and the counter. Fifty-eight percent of subjects reported no discrepancy. Based upon diary

recordings in the ITT population, 253 discrepancies were noted between diary recordings and the counter out of a total 27,037 reported actuations, which is a discrepancy rate of 0.0094 discrepancies per actuation. Based on 120 actuations in an MDI, the discrepancy rate for the ITT population was 1.12 discrepancies per 120 actuations.

As shown below in Figure 3, the majority of subjects who reported discrepancies, reported between one and three discrepancies. Overall, approximately 20% of subjects reported one discrepancy, while 6% reported two discrepancies and 8% reported 3 discrepancies. Less than 1% of subjects (2 subjects) reported more than 10 discrepancies.

Figure 3 Number of Diary Card Discrepancies per Subject (ITT Population)



Source: [N020983\S_009\2004-12-17\clinstat\SAS30033-02csr.pdf, p 318]

The most common discrepancies were count not fire (CNF) or overcounting. For the ITT population, 107 CNF discrepancies were noted out of 27,037 subject reported actuations. Based on 120 actuations in an MDI, the CNF discrepancy rate was 0.48 overcounts per 120 actuations for the ITT population.

Of particular interest are the fire not count (FNC) discrepancies or undercounting. This type of discrepancy could lead to a patient using the MDI beyond the labeled number of actuations, which presents a safety concern. Out of 27,037 subject reported actuations, 35 FNC discrepancies were noted in the ITT population. Based on 120 actuations, the FNC rate was 0.16 undercounts per 120 actuations.

Reviewer's Comment: There are no standards for discrepancy rates between patient diaries and MDI dose counters. The diary card recording is quite complex and could potentially overestimate the discrepancies. For example, some "count up unknown fire" discrepancies were noted. Counting up is mechanically impossible and most likely indicates diary card

recording errors. That being said, the diary card data indicated that the FNC rate (undercounting) was low, which is important from a safety standpoint. The patient diaries indicated that the primary discrepancies tended to be overcounting (CNF). In this reviewer's opinion, the discrepancy rates in this study are acceptable.

Table 4 summarizes the key findings for Study SAS30033 for the ITT and completer population. In general, the results were the same.

Table 4 Summary of Findings in Study SAS30033

.	Completer (N=228)			ITT Population (N=237)		
	Number of discrepancies	Discrepancies per 120 actuations	Size of discrepancy per 120 actuations	Number of discrepancies	Discrepancies per 120 actuations	Size of discrepancy per 120 actuations
Total	248	1.13	5.36	253	1.13	5.32
Count Not Fire	105	0.48	2.24	107	0.48	2.20
Count Unknown Fire	57	0.26	0.55	58	0.25	0.59
Count Up Unknown Fire	52	0.24	2.29	53	0.24	2.25
Fire Not Count	34	0.16	0.28	35	0.16	0.28

Reviewer's Comment: The Applicant also determined the count up unknown fire (CUUF) discrepancies. Counting up is mechanically impossible. Thus, the CUUF discrepancies most likely were secondary to diary entry errors. The size of the CUUF discrepancies contributed 2.25 actuations to the overall discrepancy size.

Discrepancy Size

For each discrepancy, the number of actuations that were different between the counter and patient diary is called the size of the discrepancy. Most of the discrepancy sizes were between one and two actuations. However thirteen subjects did report a discrepancy size of more than 5 actuations. Undercounting (FNC) is of particular interest because of the potential for safety issues. As shown above in Table 4, less than one actuation (0.28 actuation) per 120 actuations was undercounted.

Reviewer's Comment: Approximately 87% of discrepancies were between one and two actuations. Discrepancy sizes ranged from 1 actuation to 200 actuations. The patient diaries of the subjects who had discrepancy size of more than 5 actuations were reviewed. Many of the discrepancies were due to data entry errors or diary card recording errors. For example, the difference of 200 actuations was due to a subject entering a dose counter reading of 225, instead of 25. Therefore, the discrepancy size (or miscounts) is likely overestimated by this patient handling study.

Because of overfill of the MDI, one FNC miscount does not present a safety concern. Overfill data for fluticasone proprionate/salmeterol HFA MDI suggests that approximately 10 to 15 actuations above 120 maintain the content of fluticasone proprionate and salmeterol [NDA# 21-254, December 20, 2000, Section P10.7, Vol. 4.9, page 86].

Weight Analysis

Returned canisters were evaluated for the number of actuations based upon weight. For the ITT population, based upon canister weight, the expected mean number of actuations was 113 with a range of 109-116 actuations. The mean number of actuations based upon diary recordings was 118 and captured by the counter was 119. Based upon the weight data, there appear to have been more overcounts (CNFs).

Reviewer's Comment: It is unclear to this reviewer which is more a more reliable determination of the actual actuations used, the weight data or the patient diary data. Both sources, however, suggest that the most common type of discrepancy is overcounting.

Investigation of Devices

Devices which had a "major failure" were investigated. Mechanical findings were noted in 4% of the devices. Some of the mechanical findings, including (b) (4), damaged (b) (4) damaged (b) (4) and (b) (4), may have contributed to FNC discrepancies.

Reviewer's Comment: According to the CMC reviewer, the Applicant has optimized some of the mechanical findings, which were noted in this study. Reportedly, the optimization will not produce significant differences in the device used in this study, but should improve the counting reliability of the device.

Patient Satisfaction

Patient satisfaction surveys indicated that over 90% of subjects reported satisfaction with the counter device and indicated the counter device would help them avoid running out of medication.

Safety

Overall, the incidence of AEs was 26%. Pharyngolaryngeal pain and headache were the most common AEs. Although fluticasone proprionate/salmeterol HFA MDI is not approved, the AEs are consistent with AEs listed in the Advair Diskus product label.

Reviewer's Comment: No new safety signals were raised in this study.

Conclusion

Study SAS30033 provided clinical handling data with fluticasone proprionate/salmeterol HFA MDI with counter. There are no standards as to what is an acceptable discrepancy rate between patient diaries and MDI dose counters. The patient diary data may have overestimated discrepancies since some of the discrepancies recorded were mechanically impossible. Ideally, the dose counter should have a high level of accuracy and minimize any undercounting, as undercounting could lead to safety issues.

Study SAS30033 did not suggest any major problem with the counter. There were discrepancies between the patient diary data and the counter. The majority of the discrepancies were overcounting. Undercounting was quite low. Over the course of the life of the MDI (120 actuations), undercounting occurred less than once.

Although the counter tended to overcount, the benefits of the dose counter outweigh the potential downside of discarding the device early. Benefits include having a reliable indicator of the number of actuations remaining. Not only will patients have a better idea when a refill is needed, but patients can avoid using the product beyond the labeled use.

In this reviewer's opinion, Study SAS30033 demonstrates an acceptable level of accuracy of the dose counter based upon patient diaries. The diary card data provides clinical support to the in vitro data.

7 REVIEW OF INDIVIDUAL STUDY REPORTS

7.1 SB030003

An Open-Label, Multi-Center Study to Evaluate the Performance and Patient Satisfaction of Albuterol HFA with Counter in Asthma or COPD Subjects at Least 4 Years of Age

7.1.1 Objectives

The primary objective of this study was to evaluate the performance of albuterol HFA with counter 90 mcg in subjects with asthma or COPD. A secondary objective was to assess patient satisfaction [N020983\S_009\2004-12-17\clinstat\SB030003-04protocol.pdf, p 10].

7.1.2 Study Design

Study SB030003 was an open-label, multicenter patient handling study of albuterol HFA with counter 90 mcg in subjects with asthma or COPD.

7.1.3 Study Duration

The study commenced on May 16, 2003, and ended on December 2, 2003. The study report is dated October 24, 2004. The duration of the study was the time to complete the labeled number of actuations, approximately 50 days [N020983\S_009\2004-12-17\clinstat\SB030003-02csr.pdf, p 1-2].

7.1.4 Study Population

A total of 330 subjects were screened for the study and 268 subjects were assigned to the open-label treatment period. Subjects 4 years of age and older with a history of asthma or COPD were enrolled. In the protocol, enrollment was designed to ensure the following [N020983\S_009\2004-12-17\clinstat\SB030003-04protocol.pdf, p 18]:

- Approximately 25% of the subjects enrolled are between 4-11 years of age
- In subjects ≥ 12 years of age, approximately half of the subjects enrolled have asthma and the other half of the subjects have COPD

- Approximately 25% of the subjects (n=63) enrolled are ≥ 65 years of age.

7.1.4.1 Inclusion Criteria

The following is a list of the inclusion criteria for Study SB030003 [N020983\S_009\2004-12-17\clinstat\SB030003-04protocol.pdf, p 18-19]:

- Male or females ≥ 4 years of age
- Females are eligible only if non-pregnant and non-lactating
- Documented physician diagnosis of asthma or COPD
- Use a short acting beta agonist for relief of respiratory symptoms at least three times per week in the preceding 2 weeks
- Subjects (or parent/guardian) must have the ability to complete the diary card.

7.1.4.2 Exclusion Criteria

The following is a list of the exclusion criteria for Study SB030003 [N020983\S_009\2004-12-17\clinstat\SB030003-04protocol.pdf, p 18-22]:

- History of life-threatening asthma or COPD OR ER visit/hospitalization on two or more occasions three months prior to screening OR an ER visit/hospitalization within one month prior to screening
- Upper or lower respiratory tract, sinus, or middle ear infection that is not resolved 2 weeks prior to screening OR that occurs during screening
- History of significant concurrent disease, including, but not limited to the following: additional pulmonary disease, pneumonia within preceding month, cardiac disease, hypertension (poorly compliant with meds or frequent changes in medications), hepatic disease, renal disease requiring dialysis, PUD, neurologic disease, endocrine disorders, malignancy, psychiatric disorder, and mental retardation.
- Allergy to beta adrenergic agonist, sympathomimetic drug, or any component of the MDI formulation
- History of alcohol or drug abuse
- CXR abnormality not consistent with asthma or COPD

7.1.5 Study Centers

A total of 37 investigators in the United States participated in Study SB030003. Subjects were randomized at each of the study sites [N020983\S_009\2004-12-17\clinstat\SB030003-02csr.pdf, p 17].
Reviewer's Comment: During the course of the study, the investigator database was migrated to a new system. New investigator site numbers were generated because of this migration.

7.1.6 Materials

The following materials were utilized in Study SB030003:

- Albuterol HFA 90 mcg

- Albuterol sulfate HFA with counter 90 mcg
    - Batch numbers E03B175 and E03B499

7.1.7 Concomitant Therapy

The following medications were allowed during the study [N020983\S_009\2004-12-17\clinstat\SB030003-04protocol.pdf, p 35]**:**

- Leukotriene modifiers if started ≥ 4 weeks prior to screening
- Cromolyn or nedocromil if started ≥ 4 weeks prior to screening
- Inhaled corticosteroids if started ≥ 4 weeks prior to screening
- Intranasal corticosteroids if started ≥ 4 weeks prior to screening
- Anticholinergic agents if started ≥ 4 weeks prior to screening
- Antioxidant agents (N-acetyl-cysteine) if started ≥ 4 weeks prior to screening
- Systemic decongestants, expectorants, cough suppressants
- Topical corticosteroids
- Ophthalmic beta adrenergic antagonists
- Antihistamine, decongestants, and/or other intranasal medications for treatment of rhinitis
- Vaccinations
- Immunotherapy if started ≥ 4 weeks prior to screening and no significant change

The following medications were prohibited during the study [N020983\S_009\2004-12-17\clinstat\SB030003-04protocol.pdf, p 35-36]:

- Acute systemic corticosteroid therapy within the month prior to screening or during screening OR chronic systemic corticosteroid therapy for greater than 4 weeks within the 2 months prior to screening
- Advair must be stopped 14 days prior to screening
- Beta agonists
    - Long acting stopped 14 days prior to screening
    - Short acting discontinued prior to screening
- Antibiotic use within 2 weeks of screening or during screening
- CNS stimulants
- Oxygen
- Anti-arrhythmics
- Anticonvulsants

7.1.8 Conduct

[N020983\S_009\2004-12-17\clinstat\SB030003-04protocol.pdf, p 22-27]
The study consisted of a 7-21 day screening period followed by the open label treatment period. Eligible subjects underwent a screening period to assess compliance with study medication, diary card recording, and MDI technique. For the screening period, subjects were provided Ventolin HFA (albuterol sulfate HFA) with instructions to use on the following schedule of twice a day: 2

puffs in the morning and two puffs in the evening, approximately 12 hours apart. Subjects were to record use of the MDI on diary cards twice daily.

In order to be eligible to continue into the open label treatment period, subjects had to: 1) not have experienced an asthma or COPD exacerbation in the preceding 7 days; 2) not have experienced a URI, lower respiratory tract infection, sinus infection, or middle ear infection in the preceding 7 days; 3) demonstrated correct use of the MDI; and 4) demonstrated 90% compliance with medication usage and completion of diary card for the preceding 7 days.

Subjects who completed the screening period and continued to meet enrollment criteria were assigned to open-label albuterol HFA with counter 90 mcg (Ventolin HFA with Counter) on a scheduled dosing regimen of 2 puffs in the AM and 2 puffs in the PM (approximately 12 hours apart). Ventolin HFA was provided for rescue. The albuterol HFA with counter read 204 at the start of treatment. All subjects were instructed to prime the inhalers four times before the first use. Spacers were allowed if subjects had previously been using spacers. The duration of the study was the time to complete the labeled number of actuations, which was expected to be about 50 days.

Subjects in the open-label study period returned for clinic visits on Day 8 (Visit 3), 15 (Visit 4), 22 (Visit 5), and then biweekly until completion. A few days prior to Visit 7, the study center called the subject to coordinate the end of treatment visit date. A follow up phone call was made to the subject approximately one week after the final clinic visit (Visit 7) to assess for AEs. The following figure depicts the study schedule.

Figure 4 Study Schedule for SB030003

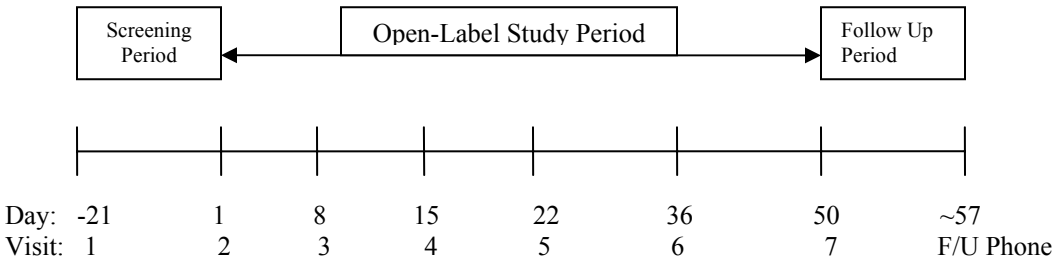


Table 5 displays the study assessments for each of the clinic visits.

Table 5 Study SB030003 Study Assessments								
Clinic Visit	1 Screening	2	3	4	5	6	7	Telephone
Days	-21 to -7	1	8 (± 3)	15 (± 3)	22 (± 3)	36 (± 3)	50 (± 3)	57 (± 3)
Informed Consent	X							
Medical History	X							
Adverse Events	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	
Review/dispense diary	X	X	X	X	X	X	X	
Patient satisfaction questionnaire		X					X	
Physical Exam	X						X	
Pregnancy test	X						X	
Check MDI use		X	X	X	X	X	X	
Dispense/collect fixed dose Ventolin HFA	X	X						
Dispense/collect Ventolin HFA with Counter		X					X	
Dispense/collect prn Ventolin HFA	X	X	X	X	X	X	X	

Source: [N020983\S_009\2004-12-17\clinstat\SB030003-04protocol.pdf, p 55]

At each clinic visit during the open label study period, AEs, concomitant medication use, and MDI use were reviewed. In addition, the diary card was reviewed and a new diary card was dispensed. The diary card data included the following information [N020983\S_009\2004-12-17\clinstat\SB030003-04protocol.pdf, p 30]:

- Counter reading before and after each dose
- Number of actuations used
- Reasons for actuations
- Written comments for any discrepancy between counter reading and actuations delivered
- Additional comments on MDI device
- AEs

Figure 5 displays a portion of the diary card.

Figure 5 Sample of Diary Card

Day	Date[1] Month Day Year	Counter reading prior to this use[2]	Comment if counter readings do not match following the last use and prior to this use[3]	Total number of puffs following this use[4]	Counter reading following this use[5]	Reason puffs delivered[6] 1 = AM dosing 2 = PM dosing 3 = Priming 4 = Cleaning OT = Other, specify	Comment if counter reading does not change by number of puffs delivered following this use[7]
e.g.,	03 / 15 / 03	204		4	200	3	
e.g.,	03 / 15 / 03	200		2	198	2	
e.g.,	03 / 16 / 03	195	dropped inhaler on floor	2	193	1	
e.g.,	03 / 16 / 03	193		2	189	OT, test spray	dropped inhaler after use
1	/ /						
2	/ /						
3	/ /						
4	/ /						
5	/ /						

Source: [N020983\S_009\2004-12-17\clinstat\SB030003-05crfs.pdf, p 65]

Patient satisfaction questionnaires were collected on Day 1 and the final study visit. Subjects rated their satisfaction with albuterol HFA with counter. Satisfaction ratings were measured on a 5 point scale, with higher scores indicating higher satisfaction. In addition, subjects were asked to agree/disagree with statements regarding their continued use of albuterol HFA with counter [N020983\S_009\2004-12-17\clinstat\SB030003-04protocol.pdf, p 30].
Reviewer's Comment: The patient satisfaction questionnaire is not a validated patient reported outcome instrument.

7.1.8.1 Study Withdrawals

If subjects were not compliant with diary card completion (< 90% completion) or albuterol HFA with counter use (< 90% use), subjects were counseled on appropriate collection of diary card recording and medication use. If the subject remained non-compliant, the subject was withdrawn from the study [N020983\S_009\2004-12-17\clinstat\SB030003-04protocol.pdf, p 25].

Subjects were withdrawn from the study due to worsening asthma or COPD, such as an exacerbations requiring ER visit, hospitalization, or use of a prohibited asthma or COPD medication. Asthma or COPD exacerbations were not recorded as adverse events, unless they met the definition of an SAE [N020983\S_009\2004-12-17\clinstat\SB030003-04protocol.pdf, p 28].

Subjects were also withdrawn for adverse events, which posed an unacceptable risk in the investigator's opinion [N020983\S_009\2004-12-17\clinstat\SB030003-04protocol.pdf, p 36].

7.1.9 Data Analysis

The Completer Population was the Applicant's pre-specified primary population of interest and was defined as all subjects who recorded 90% (180) of the labeled actuations (200) of albuterol

HFA with counter on the diary card. The Intent-to-Treat Population was defined as all subjects who received at least one actuation of albuterol HFA with counter. The Total Population was defined as all subjects who were screened. The Screen Failure Population was defined as all subjects screened, but discontinued prior to open-label study assignment [N020983\S_009\2004-12-17\clinstat\SB03003-04protocol.pdf, p 45].
Reviewer's Comment: Although the Applicant pre-specified the completer population as its primary population of interest, results for the ITT population were reviewed. The results for the total population and screen failure population are not addressed in this review.

An ITT impact analysis was conducted a posteriori with data for all subjects in the ITT population but excluding data points where values were provided after the counter reached zero, out of range data, impossible values, or significant data entry errors were noted [N020983\S_009\2004-12-17\clinstat\SB030003-02csr.pdf, p 42].
Reviewer's Comment: The ITT impact analyses were interpreted with caution because it is a post hoc analysis.

No statistical hypothesis testing was performed because this was an open-label single arm study. Pre-specified dose counter evaluation variables included the following:

- Diary card recorded actuations
- Diary card recorded MDI counter readings
- Canister weight
- Results of investigations into subject-reported problems with MDI counter

Subject's satisfaction with albuterol HFA with counter was summarized [N020983\S_009\2004-12-17\clinstat\SB030003-04protocol.pdf, p 46].

7.1.10 Amendments

One amendment was made to the original protocol on June 20, 2003. The amendment provided for revisions/clarifications of the enrollment criteria, extension of the screening period from 7-10 days to 7-21 days, addition of phone contact between Visit 6 and 7, and clarification of permitted and prohibited medications [N020983\S_009\2004-12-17\clinstat\SB030003-04protocol.pdf, p 63-67].

7.1.11 Results

7.1.11.1 Subject Disposition

A total of 330 subjects were screened for Study SB030003 and 268 were assigned to open label treatment. As discussed above, four populations were pre-specified in the protocol. The Total Population was defined as all subjects who were screened, thus the Total Population was 330. The ITT Population was defined as all subjects who received at least one actuation of albuterol HFA with counter, thus the ITT Population was 268. The Completer Population was the Applicant's pre-specified primary population of interest and was defined as all subjects who recorded at least 90% of the labeled actuations of albuterol HFA with counter (at least 180 out of

200) on the diary card. The Completer Population was 224. The Intent to Treat Impact Analysis Population was 266.

The main reason that subjects who underwent the screening period were not assigned to the open label treatment period was that the age or disease strata was closed. Table 6 displays the subject disposition for the screening period.

Table 6 Subject Disposition for Screening Period in Study SB030003 (Total Population)

	Screening Period, n (%)
Enrolled	330
Discontinued	62 (19)
No documented diagnosis of asthma or COPD	1 (<1)
Consent withdrawn	3 (<1)
Did not fulfill eligibility criteria	1 (<1)
Prohibited medication use	3 (<1)
History of significant disease	3 (<1)
Recent infection	2 (<1)
Adverse event	5 (2)
Unspecified (failed to complete diary)	7 (2)
Other	41 (12)
Assigned to open-label treatment	268 (81)

Source [N020983\S_009\2004-12-17\clinstat\SB030003-02csr.pdf, p 56]

Reviewer's Comment: The majority of the "other" category was secondary to closure of age strata.

Overall 241 (90%) of subjects assigned to open-label treatment completed the study. Table 7 displays subject disposition for the open-label treatment period by age strata. This number is different from the number of subjects in the pre-specified completer population, which was 224. The completer population was defined as subjects who recorded 90% of the labeled actuations (at least 180) of albuterol HFA with counter on the diary card.

Reviewer's Comment: It is possible to have completed the study, but not have recorded 180 actuations on the diary card.

Table 7 Subject Disposition by Age Strata for Study SB030003 (ITT Population)

	Age 4-11 N= 78 n (%)	Age 12-64 N=129 n(%)	Age ≥ 65 N=61 n (%)	Total N=268 n(%)
Assigned to open-label treatment	78	129	61	268
Completed	74 (95)	114 (88)	53 (87)	241 (90)
Discontinued	4 (5)	15 (12)	8 (13)	27 (10)
AE	0	2 (2)	2 (3)	4 (1)
Voluntary withdrawal	0	3 (2)	0	3 (1)
Lost to follow-up	1 (1)	3 (2)	0	4 (1)
Protocol Violation	0	1 (<1)	0	1 (<1)
Exacerbation	2 (3)	4 (3)	3 (5)	9 (3)
Non-compliance	1 (1)	1 (<1)	2 (3)	4 (1)
Other	0	1 (<1)	1 (2)	2 (<1)

Source [N020983\S_009\2004-12-17\clinstat\SB030003-02csr.pdf, p 57]

Reviewer's Comment: The study was designed to enroll >25% of subjects in the 4-11 years of age range and >25% of subjects in the ≥65 years of age range. For the open-label treatment period, Study SB030003 had 29% of subjects in the 4-11 years of age range and 20% of subjects in the ≥ 65 years of age range.

Reviewer's Comment: The Applicant also presented subject disposition by disease – asthma and COPD. Six percent of subjects with asthma discontinued the study versus 15% of subjects with COPD. The most common reason for subject discontinuation was exacerbation. Two percent of subjects with asthma discontinued due to exacerbation, while 5% of subjects with COPD discontinued due to exacerbation.

Approximately 50% of the subjects had protocol deviations during the study. The most common reason for protocol deviations was the "other" category, which included study visits outside the protocol-defined windows and failure to make follow-up phone calls. Additional common protocol violations included non-compliance with study procedures after enrollment [N020983\S_009\2004-12-17\clinstat\SB030003-02csr.pdf, p 59].

7.1.11.2 Demographics and Baseline Characteristics

The majority of subjects in Study SB030003 were caucasian. The mean age was 39, with an age range of 4 to 90 years. There was a higher percentage of subjects with asthma (59%) versus COPD (41%). Table 8 displays the demographics and baseline characteristics of the study population in Study SB0300033.

Table 8 Demographics and Baseline Characteristics in Study SB030003 ITT Population				
	Age 4-11 N= 78 n (%)	**Age 12-64 N=129 n(%)**	**Age ≥ 65 N=61 n (%)**	**Total N=268 n(%)**
Gender				
Male	36 (46)	49 (38)	39 (64)	124 (46)
Female	42 (54)	80 (62)	22 (36)	144 (54)
Age				
Mean (Range)	8.1 (4-11)	42 (13-64)	71 (65-90)	39 (4-90)
Race				
Caucasian	59 (76)	112 (87)	58 (95)	229 (85)
Black	9 (12)	8 (6)	3 (5)	20 (7)
Hispanic	6 (8)	2 (2)	0	8 (3)
Asian	1 (1)	4 (3)	0	5 (2)
North African	1 (1)	0	0	1 (<1)
Other	2 (3)	3 (2)	0	5 (2)
Disease group				
Asthma	78 (100)	73 (57)	7 (11)	158 (59)
COPD	0	56 (43)	54 (89)	110 (41)

Source [N020983\S_009\2004-12-17\clinstat\SB030003-02csr.pdf, p 60]

Reviewer's Comment: There are no subjects in the 4-11 age range with COPD, which is appropriate since COPD is predominantly a disease of adults.

Reviewer's Comment: The Applicant also presented the baseline characteristics and demographics for the completer population. One notable point is that the completer population had a larger percentage of subjects with asthma (61%) versus COPD (39%). This may in part be due to the fact that more subjects with COPD discontinued because of exacerbation.

Reviewer's Comment: The Applicant presented the baseline characteristics by disease strata. As expected the asthma population was younger (mean age 23 years) than the COPD population (mean age 63 years). Approximately half of the COPD population was ≥ 65 years of age.

7.1.11.3 Study Endpoints

No efficacy parameters were measured during this open-label single arm study. The Applicant evaluated the pre-specified study endpoints using the ITT population and the completer population. The data will be presented for the completer population. However, since the results for the ITT population are important, significant differences in the results for the ITT population and the completer population will be noted. A table of the pertinent results for both populations is included towards the end of the review.

There were 224 subjects in the completer population and 268 in the ITT population. In the ITT population, one subject had no follow up, so the results for the ITT population are based upon 267 subjects.

The Applicant presented the diary card data in quartiles to determine concordance with the dose counter over the life of the device. A "handling" is defined as each row of the diary data recorded during each dosing from the device. Overall, of the 22,047 subject reported handlings, only 95 handlings had missing diary data. Table 9 displays the patient handlings and actuations for the completer population in Study SB030003. In this table, for each counter reading quartile, there would typically be approximately 25 handlings (50 actuations) per subject.

Table 9 Diary Card Summary of Reported Handlings and Actuations Study SB030003 Completer Population

	Counter Reading 151-200	Counter Reading 101-150	Counter Reading 51-100	Counter Reading 0-50	Total
Number of subjects	224	224	224	224	224
Total subject reported handlings[1]	5580	5549	5567	5325	22,047
Number of handlings with missing diary data[2]	24	23	14	8	95
Number of handlings with no missing diary data	5556	5526	5553	5317	21,952
Total number of subject reported actuations[3]	11,089	11,056	11,109	10,611	43,865

1 A "handling" is each row of the diary data recorded during each dosing from the device. For each counter reading category, there would typically be approximately 25 handlings (50 actuations) per subject.
2 Record is missing for concordance purposes if any recorded or derived information for that record is missing
3 Total reported actuations is based upon non-missing handlings and is the sum of PUFFNUM from diary data
Source: [N020983\S_009\2004-12-17\clinstat\SB030003-02csr.pdf, p 69]

Reviewer's Comment: The total number of subject reported actuations in the ITT population was 48,721.

The following definitions were pre-specified in the protocol and utilized throughout the study report to describe the diary data discrepancies:

- Derived pre-use MDI count - Diary card reading "counter reading following use" for preceding entry
- Derived post-use MDI count - Diary card reading "counter reading prior to this use – total number of puffs following this use"
- Derived number of actuations – Diary card reading "counter reading prior to this use" – "counter reading following this use"

Reviewer's Comment: Figure 5 displays a section of the diary card. Counter reading prior to this use, the number of actuations, and counter reading following this use were recorded. The derived definitions above were determined from the diary card data for analyses purposes. If the derived pre-use MDI count and derived post-use MDI count did not match the reported pre-use MDI count and reported post-use MDI count, respectively, this was considered a discrepancy.

- Count Not Fire (CNF) - The value of 'Counter reading following this use' was lower than the 'Derived Post-use MDI Count'
- Count Unknown Fire (CUF) – The value of 'Counter reading prior to this use' was lower than the 'Derived Pre-use MDI Count'

- Count Up Unknown Fire (CUUF) - The value of 'Counter reading prior to this use' was higher than the 'Derived Pre-use MDI Count'

Reviewer's Comment: According to the Applicant, CUUF, is mechanically impossible and likely due to patient data errors.

- Fire Not Count (FNC) - If the value of 'Counter reading following this use' was higher than the 'Derived Post-use MDI Count'

Reviewer's Comment: In meetings with the Applicant, the Division conveyed that ideally discrepancies for either category would be minimal. However, if discrepancies do occur, 'count not fire' is preferable to 'fire not count'. That is, it is preferable to have the dose counter overcount a small amount and the inhaler refilled prematurely than to have the dose counter undercount and the patient continue to use the inhaler beyond the labeled number of actuations. This latter discrepancy (fire not count) presents a safety issue.

Of the 21,952 recorded device handlings without missing diary data, 333 discrepancies were noted, which equates to a diary card discrepancy rate of 1.52 discrepancies per 100 handlings. The majority of the discrepancies noted were count not fire (CNF), followed by count unknown fire (CUF), fire not count (FNC), and count up unknown fire (CUUF). Table 10 displays the diary card discrepancies for the completer population.

Table 10 Diary Card Discrepancies and Discrepancy Rate Study SB030003 Completer Population

	Counter Reading 151-200	Counter Reading 101-150	Counter Reading 51-100	Counter Reading 0-50	Total
Number of subjects	224	224	224	224	224
Number of handlings with no missing diary data	5556	5526	5553	5317	21,952
Total number of diary card discrepancies	103	102	63	65	333
Count not fire (CNF)	53	45	38	37	173
Count unknown fire (CUF)	35	39	14	15	103
Count up unknown fire (CUUF)	6	9	2	2	19
Fire not count (FNC)	9	9	9	11	38
Diary card discrepancy rate per 100 handlings	1.85	1.85	1.13	1.22	1.52
Count not fire (CNF)	0.95	0.81	0.68	0.70	0.79
Count unknown fire (CUF)	0.63	0.71	0.25	0.28	0.47
Count up unknown fire (CUUF)	0.11	0.16	0.04	0.04	0.09
Fire not count (FNC)	0.16	0.16	0.16	0.21	0.17

Source: [N020983\S_009\2004-12-17\clinstat\SB030003-02csr.pdf, p 71]

Reviewer's Comment: For the ITT population, the overall number of discrepancies was 471, which is a diary card discrepancy rate of 1.93 per 100 handlings. For the ITT population, the CNF, CUF, CUUF, FNC rate were 0.86, 0.75, 0.11, and 0.21, respectively, per 100 handlings.

The most common discrepancy was count not fire or overcounts. FNC miscounts are of particular interest due to the potential safety concerns. The overall FNC rate was 0.17 FNC discrepancies per 100 recorded handlings. Fire not count discrepancies occurred at a similar rate

across the life of the device, whereas other discrepancy rates were highest during the first half of the life of the device.

The Applicant determined the discrepancy rate per 100 actuations, as shown below in Table 11. Since two actuations per handling were specified, the discrepancy rate per100 actuations was approximately half of the discrepancy rate per 100 handlings. The most common discrepancy was count not fire. The FNC discrepancy rate was 0.09 FNC discrepancies per 100 reported actuations.

Table 11 Diary Card Actuations and Discrepancy Rate per Actuations Study SB030003 Completer Population

	Counter Reading 151-200	Counter Reading 101-150	Counter Reading 51-100	Counter Reading 0-50	Total
Number of subjects	224	224	224	224	224
Number of handlings with no missing diary data	5556	5526	5553	5317	21,952
Total number of subject reported actuations	11,089	11,056	11,109	10,611	43,865
Total number of diary card discrepancies	103	102	63	65	333
Count not fire (CNF)	53	45	38	37	173
Count unknown fire (CUF)	35	39	14	15	103
Count up unknown fire (CUUF)	6	9	2	2	19
Fire not count (FNC)	9	9	9	11	38
Diary card discrepancy rate per 100 actuations	0.93	0.92	0.57	0.61	0.76
Count not fire (CNF)	0.48	0.41	0.34	0.35	0.39
Count unknown fire (CUF)	0.32	0.35	0.13	0.14	0.23
Count up unknown fire (CUUF)	0.05	0.08	0.02	0.02	0.04
Fire not count (FNC)	0.08	0.08	0.08	0.10	0.09

Source: [N020983\S_009\2004-12-17\clinstat\SB030003-02csr.pdf, p 73]

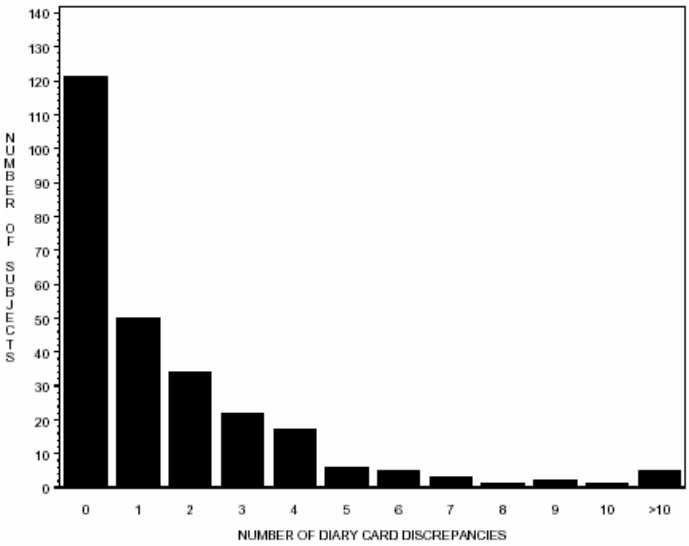
Reviewer's Comment: For the ITT population, the overall diary card discrepancy rate per 100 actuations was 0.97 per 100 actuations. The CNF, CUF, CUUF, FNC rate were 0.43, 0.38, 0.06, and 0.10, respectively, per 100 actuations.

For the completer population, 47% of subjects did not have any discrepancies between diary recordings and the counter readings. Approximately 18% of subjects noted one discrepancy, 13% noted two discrepancies, 8% noted three discrepancies, and 7% noted four discrepancies. More than four discrepancies were noted, but in less than 3% of subjects. One subject reported 20 discrepancies (Subject 432) [N020983\S_009\2004-12-17\clinstat\SB030003-02csr.pdf, p 76].

Reviewer's Comment: In the ITT Population, the distribution of discrepancies was similar except five subjects reported >10 discrepancies. Subjects 178, 179, 534, 432, and 717 reported 11, 12, 14, 20, and 45 discrepancies, respectively. As shown below in Figure 6, the majority of subjects who reported discrepancies, reported between one and four discrepancies. Overall, approximately 30% of subjects reported one to two discrepancies, while 2% of subjects (5 subjects) reported more than 10 discrepancies.

The subject with 45 discrepancies was noted to have difficulty following diary card instruction and was discontinued from the study on day 28. The subject was noted to continue to take medication for 7 days after the counter reached '000', which contributed to some of the discrepancies [N020983\S_009\2004-12-17\clinstat\SB030003-02csr.pdf, p 1041].

Figure 6 Number of Diary Card Discrepancies per Subject (ITT Population)



Source: [N020983\S_009\2004-12-17\clinstat\SB030003-02csr.pdf, p 344]

Of the 333 noted discrepancies between diary cards and counter readings, the majority of the discrepancy sizes were between one or two actuations as shown below in Table 12. Discrepancy sizes between the diary card and counter readings ranged from 1 actuation to 100 actuations.

Table 12 Diary Card Summary of Discrepancy Size Study SB030003 Completer Population

	Count Not Fire (CNF)	Count Unknown Fire (CUF)	Count Up Unknown Fire (CUUF)	Fire Not Count (FNC)	All Categories
Total discrepancies	173	103	19	38	333
Discrepancy Size, n (%)					
1	140 (81)	17 (17)	1 (5)	11 (29)	169 (51)
2	26 (15)	58 (56)	14 (74)	26 (68)	124 (37)
3	3 (2)	10 (10)	0	1 (3)	14 (4)
4	2 (1)	12 (12)	0	0	14 (4)
5	0	1 (<1)	1 (5)	0	2 (<1)
>5	2 (1)	5 (5)	3 (16)	0	10 (3)

Source: [N020983\S_009\2004-12-17\clinstat\SB030003-02csr.pdf, p 77]

Reviewer's Comment: There were 471 total discrepancies in the ITT Population. In the ITT Population, 42% of the discrepancies were one actuation and 46% were two actuations. Four percent (19) of the discrepancies were >5 actuations. The patient diaries of the subjects who

had discrepancy size of more than 5 actuations were reviewed. Many of the discrepancies were due to data entry errors or diary card recording errors. Therefore, the discrepancy size (or miscounts) is likely overestimated by this patient handling study.

The Applicant determined the discrepancy size per 200 reported actuations as follows. The diary card discrepancy sizes were summed and multiplied by 100 then divided by the total reported actuations for nonmissing data. This value was then multiplied by 2.0 to report the discrepancy size based on a recommended 200 actuation canister. The discrepancy size per 200 actuations is shown below in Table 13.

Table 13 Diary Card Summary Discrepancy Size per 200 Actuations[1] Study SB030003 Completer Population

	Number of Discrepancies	Sum of Discrepancy Sizes	Discrepancy Size per 200 Reported Actuations[1]
Count Not Fire	173	223	1.02
Count Unknown Fire	103	396	1.81
Count Up Unknown Fire	19	213	0.97
Fire Not Count	38	66	0.30
All Discrepancies	333	898	4.09

Source: [N020983\S_009\2004-12-17\clinstat\SB030003-02csr.pdf, p 78]
1 The discrepancy size per 200 reported actuations is the sum of the diary card discrepancy sizes multiplied by 100 then divided by the total reported actuations for nonmissing data. This value was then multiplied by 2.0 to report the data based on a recommended 200 actuation canister size.

Reviewer's Comment: For the ITT population, the total discrepancy size per 200 actuations was 5.78 actuations. The CNF, CUF, CUUF, and FNC discrepancy sizes per 200 actuations were 1.13, 2.77, 1.53, and 0.34 actuations, respectively.

Reviewer's Comment: The FNC or undercounting discrepancy size is less than one actuation.

The Applicant performed an "ITT Impact Analyses" post hoc. The population included all subjects in the ITT Population but excluded or corrected data points where values were provided after the counter reached zero, out of range data, impossible values, or significant data entry errors were noted. The Applicant corrected data rows for 6 subjects and excluded data rows for 10 subjects. The majority of the data points deleted were diary records after the device reached zero. All data for subject 717 was deleted for the ITT impact analyses as the subject had 14 diary records after the device reached zero and also had other diary compliance issues. Thus the total number of subjects in the ITT impact analyses was 266 [N020983\S_009\2004-12-17\clinstat\SB030003-02csr.pdf, p 80-81].

Reviewer's Comment: The post hoc ITT impact analyses should be interpreted with caution. Therefore, the entirety of the data is not presented here. The results do not differ a significant amount from the results of the ITT population. Overall, there were 410 diary discrepancies (471 in ITT) with 0.85 discrepancies per 100 actuations (0.97 in ITT). Count not fire was the most common discrepancy with fire not count the least common discrepancy. The discrepancy size per 200 actuations was 5.18 actuations, of which 2.39 were CUF, 1.40 were CUUF, 1.12 were CNF, and 0.27 were FNC.

Subgroup analyses by age, disease, and gender were performed. For age subgroup analyses, age groups were 4-11 years, 12-64 years, and ≥65 years. Table 14 displays the data from the Applicant's subgroup analyses.

Table 14 Subgroup Analyses for Completer Population – Study SB030003

	Completer Population		
Number of Subjects	N = 224		
Total Number of Diary Card Discrepancies (rate per 100 actuations), size per 200 actuations	333 (0.76) 4.09		
Count Not Fire (CNF)	173 (0.39) 1.02		
Count Unknown Fire (CUF)	103 (0.23) 1.81		
Count Up Unknown Fire (CUUF)	19 (0.04) 0.97		
Fire Not Count (FNC)	38 (0.09) 0.30		
	Age		
	4-11 Years	12-64 Years	≥65 Years
Number of Subjects	N = 69	105	N = 50
Total Number of Diary Card Discrepancies (rate per 100 actuations), size per 200 actuations	160 (1.19) 4.25	132 (0.64) 5.04	41 (0.42) 1.91
Count Not Fire (CNF)	89 (0.66) 1.77	61 (0.30) 0.69	23 (0.23) 0.67
Count Unknown Fire (CUF)	48 (0.36) 1.86	46 (0.22) 2.48	9 (0.09) 0.32
Count Up Unknown Fire (CUUF)	6 (0.04) 0.16	7 (0.03) 1.58	6 (0.06) 0.79
Fire Not Count (FNC)	17 (0.13) 0.45	18 (0.09) 0.29	3 (0.03) 0.12
	Disease		
	Asthma	COPD	
Number of Subjects	N = 137	N = 87	
Total Number of Diary Card Discrepancies (rate per 100 actuations), size per 200 actuations	230 (0.86) 4.46	103 (0.60) 3.52	
Count Not Fire (CNF)	120 (0.45) 1.16	53 (0.31) 0.80	
Count Unknown Fire (CUF)	71 (0.27) 2.04	32 (0.19) 1.44	
Count Up Unknown Fire (CUUF)	10 (0.04) 0.90	9 (0.05) 1.09	
Fire Not Count (FNC)	29 (0.11) 0.37	9 (0.05) 0.20	
	Gender		
	Females	Males	
Number of Subjects	N = 124	N = 100	
Total Number of Diary Card Discrepancies (rate per 100 actuations), size per 200 actuations	202 (0.83) 3.86	131 (0.67) 4.39	
Count Not Fire (CNF)	108 (0.44) 1.08	65 (0.33) 0.93	
Count Unknown Fire (CUF)	56 (0.23) 1.61	47 (0.24) 2.05	
Count Up Unknown Fire (CUUF)	11 (0.05) 0.81	8 (0.04) 1.17	
Fire Not Count (FNC)	27 (0.11) 0.36	11 (0.06) 0.23	

Source: [N020983\S_009\2004-12-17\clinstat\SB030003-02csr.pdf, p 83]

Discrepancies occurred at a lower rate in the 12-64 years (0.64 per 100 actuations) and ≥65 years age range (0.42 per 100 actuations) compared to the 4-11 years age range (1.19 per 100 actuations). Count not fire and count unknown fire were the most common discrepancies in all age ranges. The rates of the different categories of discrepancies appeared proportional between

age groups. Discrepancy size was less in the ≥65 years age group with 1.91 actuations per 200 actuations.

The disease subgroups consisted of subjects with asthma and subjects with COPD. There were fewer subjects with COPD. There was a lower rate of discrepancies (0.60 per 100 actuations) and smaller size of discrepancies (3.52 actuations per 200 actuations) in the COPD population compared to the asthma population (discrepancy rate of 0.86 per 100 actuations and discrepancy size of 4.46 actuations per 200 actuations). As in the total population, count not fire was the most common discrepancy and fire not count was less common.

Although discrepancies occurred at a slightly higher rate in females (0.83 per 100 actuations) than in males (0.67 per 100 actuations), the size of the discrepancy was larger in males 4.39 per 200 actuations compared to females with 3.86 actuations per 200 actuations.

For completeness, the subgroup analyses for the ITT population are shown below in Table 15. The discrepancies were slightly higher in the ITT population compared to the completer population, but the subgroup patterns were consistent with the completer population. The ≥65 years group had a lower rate of discrepancies than the other age ranges. Discrepancy rates were similar in the asthma and COPD population. As in the completer population, the size of the discrepancy was smaller in the COPD subgroup than in the asthma subgroup.

Table 15 Subgroup Analyses for ITT Population – Study SB030003

	ITT Population		
Number of Subjects	N = 267[1]		
Total Number of Diary Card Discrepancies (rate per 100 actuations), size per 200 actuations	471 (0.97) 5.78		
Count Not Fire (CNF)	209 (0.43) 1.13		
Count Unknown Fire (CUF)	184 (0.38) 2.77		
Count Up Unknown Fire (CUUF)	28 (0.06) 1.53		
Fire Not Count (FNC)	50 (0.10) 0.34		
	Age		
	4-11 Years	12-64 Years	≥65 Years
Number of Subjects	N = 78	128	N = 61
Total Number of Diary Card Discrepancies (rate per 100 actuations), size per 200 actuations	193 (1.32) 6.03	213 (0.91) 7.05	65 (0.60) 2.66
Count Not Fire (CNF)	94 (0.64) 1.73	78 (0.33) 0.80	37 (0.34) 1.06
Count Unknown Fire (CUF)	72 (0.49) 2.38	98 (0.42) 4.03	14 (0.13) 0.54
Count Up Unknown Fire (CUUF)	9 (0.06) 1.48	9 (0.04) 1.84	10 (0.09) 0.93
Fire Not Count (FNC)	18 (0.12) 0.44	28 (0.12) 0.39	4 (0.04) 0.13
	Disease		
	Asthma	COPD	
Number of Subjects	N = 157	N = 110	
Total Number of Diary Card Discrepancies (rate per 100 actuations), size per 200 actuations	284 (0.96) 6.36	187 (0.97) 4.88	
Count Not Fire (CNF)	133 (0.45) 1.15	76 (0.39) 1.10	
Count Unknown Fire (CUF)	103 (0.35) 3.01	81 (0.42) 2.39	
Count Up Unknown Fire (CUUF)	14 (0.05) 1.81	14 (0.07) 1.10	
Fire Not Count (FNC)	34 (0.12) 0.38	16 (0.08) 0.29	
	Gender		
	Females	Males	
Number of Subjects	N = 143	N = 124	
Total Number of Diary Card Discrepancies (rate per 100 actuations), size per 200 actuations	229 (0.86) 4.84	242 (1.09) 6.90	
Count Not Fire (CNF)	117 (0.44) 1.10	92 (0.42) 1.18	
Count Unknown Fire (CUF)	66 (0.25) 2.13	118 (0.53) 3.53	
Count Up Unknown Fire (CUUF)	14 (0.05) 1.22	14 (0.06) 1.91	
Fire Not Count (FNC)	32 (0.12) 0.39	18 (0.08) 0.29	

Source: [N020983\S_009\2004-12-17\clinstat\SB030003-02csr.pdf, p 83]

Diary card comments were not common during the study (<2% of handlings). Comments prior to handling included: dropped canister, accidental actuation, misfire, missed doses, or unknown. Comments after use included: dropped canister, child playing with canister, no medication delivered, forgot/missed dose, and unknown [N020983\S_009\2004-12-17\clinstat\SB030003-02csr.pdf, p 88].

The Applicant weighed the canisters prior to shipping to the study site and on return of the canister from the study site. Two batches of study medication were used for this study: E03B126

and E03B499. However, only one canister was from batch E03B499 and the subject did not return the canister. Thus, all the data pertains to batch E03B126. For the completer population, the mean weight prior to shipping was 42.3g. The mean weight upon return was 29.5g. The mean difference was 13.4 g. The mean weight per actuation for batch E03B126 was 72.63mg (+/- 0.68 mg). Thus the expected mean number of actuations used based upon canister weight was 184 with a range of 180-189 actuations. The mean number of actuations used based upon subject reported actuations was 200 [N020983\S_009\2004-12-17\clinstat\SB030003-02csr.pdf, p 89-90].
Reviewer's Comment: For the ITT population, the expected mean number of actuations based upon weight was 174 with a range of 170-178. The mean number of actuations captured by the counter and based upon subject reported actuations was 190 and 188, respectively.
Reviewer's Comment: The weight data suggests that the counter tended to overcount.

Reviewer's Comment: Four subjects in the ITT population were noted to have significant discrepancies between the numbers of actuations based upon weight compared to the number of actuations based upon diary recordings. Two were non-compliant with diary recording and study medication. For one subject, the weight data supported less actuations than the diary and counter data. For one subject, the recorded actuations and counter reading were consistent with the weight data; however, the investigator reported counter reading showed fewer actuations were used. It is unclear how this could happen.

According to the protocol, any MDI with Counter device experiencing a "major failure" was investigated. Device
major failure for this study included:

- Any instance of Fire Not Count (FNC)
- Total diary card discrepancy size between recorded actuations and counter reading greater than the range tolerance (±8 actuations)
- Any situation as deemed necessary by the study team.

Investigation included analyzing discrepancies, visual, microscopic, and x-ray assessments [N020983\S_009\2004-12-17\clinstat\SB030003-02csr.pdf, p 91].

Of the 268 devices used by subjects, 61 devices met the criteria for investigation and 36 devices were analyzed. Twenty-five were not analyzed for the following reasons: evidence of misuse (9), device not returned (5), missing diary data (5), database entry errors (5), and subject dropped from study due to non-compliance (1). Of the 25 analyzed, 16 had some mechanical finding, 5 of which were deemed a potential cause of the discrepancy. Mechanical defect categories included: (b) (4) [N020983\S_009\2004-12-17\clinstat\SB030003-02csr.pdf, p 92-93].
Reviewer's Comment: At least 6% (16/268) of the devices used in the study had mechanical findings and at least 2% (5/268) of the devices had mechanical findings as a potential cause of discrepancies.

Patient satisfaction surveys were collected by the Applicant. Subject satisfaction was based on a five point scale, with higher scores indicating increased satisfaction with therapy. At baseline,

the majority of subjects reported anxiety about not knowing how much medication remained. Subjects reported a variety of methods to determine how much medication remained. Over 90% of subjects reported satisfaction with the counter device and indicated the counter device would help them avoid running out of medication.
Reviewer's comment: The patient satisfaction survey is not a validated PRO instrument.

7.1.11.4 Safety

Safety data is presented for the ITT population. Approximately 88% of subjects were exposed to albuterol HFA with counter for >43 days. The mean number of days of exposure was 47 days. The youngest age group had the highest mean number of days of exposure at 48 days and the oldest age group had the lowest mean number of days of exposure at 45 days. Subjects with COPD had slightly lower mean days of exposure at 45 compared to subjects with asthma at 48 days [N020983\S_009\2004-12-17\clinstat\SB030003-02csr.pdf, p 103-104].
Reviewer's Comment: The slight difference in exposure is unlikely to influence the results of the study.

There were no deaths reported in this study. No SAEs were reported during the treatment phase of the study, but one SAE was reported during the screening phase of the study. One subject with a history of CVA on warfarin therapy developed rectal bleeding and required admission to the ICU. The event resolved and the patient was discharged from the hospital [N020983\S_009\2004-12-17\clinstat\SB030003-02csr.pdf, p 112].
Reviewer's Comment: The patient was over anti-coagulated with an INR of 12.3 when admitted to the hospital. This seems to be a major contributing factor to the rectal bleeding.

Five subjects were withdrawn from the study for the following adverse events: viral upper respiratory tract infection and asthma exacerbation, acute sinusitis, bronchitis, sinusitis, and upper respiratory tract infection [N020983\S_009\2004-12-17\clinstat\SB030003-02csr.pdf, p 114].

A total of 83 subjects (31%) reported at least one AE during the treatment period. Common adverse events noted in Study SB030003 are shown below in Table 16. Cough, pharyngolaryngeal pain , headaches, and pyrexia were the most common AEs reported. In general AEs were more common in the 4-11 years age group. AEs were more common in the 4-11 years age range.

Table 16 Adverse Events Occurring at an Incidence ≥3% During the Treatment Period by Age Strata in Study SB030003 ITT Population				
	Age 4-11 N= 78 n (%)	**Age 12-64 N=129 n(%)**	**Age ≥ 65 N=61 n (%)**	**Total N=268 n(%)**
Any Event	28 (36)	41 (32)	14 (23)	83 (31)
Respiratory, thoracic disorders				
Any Event	13 (17)	13 (10)	4 (7)	30 (11)
Cough	5 (6)	4 (3)	0	9 (3)
Pharyngolaryngeal pain	4 (5)	4 (3)	1 (2)	9 (3)
Nervous system disorders				
Any Event	5 (6)	6 (5)	2 (3)	13 (5)
Headache	5 (6)	2 (2)	2 (3)	9 (3)
General disorders				
Any Event	7 (9)	3 (2)	1 (2)	11 (4)
Pyrexia	6 (8)	2 (2)	0	8 (3)

Source: [N020983\S_009\2004-12-17\clinstat\SB030003-02csr.pdf, p 106]

Thirteen subjects experienced a COPD (8) or asthma (5) exacerbation during the study. The most common reported cause of exacerbation was respiratory infection. Nine of the thirteen subjects were withdrawn from the study, while the other four continued in the study, which was a protocol violation [N020983\S_009\2004-12-17\clinstat\SB030003-02csr.pdf, p 117].

7.1.12 Conclusions

In Study SB030003, 268 subjects were assigned to open-label treatment with albuterol HFA MDI with counter following a screening period. The majority of subjects (224) recorded at least 180 actuations on the diary card. This population was defined as the completer population.

Overall, there was a high level of concordance between the recorded actuations in the diary and indicated by the counter. Based upon diary recordings in the completer population, 333 discrepancies were noted with the counter out of a total 43,865 reported actuations. The rate of discrepancies was 1.52 discrepancies per 200 actuations. In the ITT population, the overall discrepancy rate per 200 actuations was 1.95 discrepancies per 200 actuations.

The most common discrepancies were CNF or overcounts. For the completer population, 173 CNF discrepancies were noted out of 43,865 subject reported actuations without missing diary data. In the ITT population, the CNF rate per 200 actuations was 0.86 CNF discrepancies per 200 actuations. Of particular interest are the FNC discrepancies, which uncommon. In the ITT population, the FNC rate per 200 actuations was 0.20 FNC discrepancies per 200 actuations.

For the ITT population, the size of the discrepancies was 5.78 actuations per 200 actuations. The size of the undercounting or FNC discrepancies was less than one actuation. Returned cannisters were evaluated for the number of actuations based upon weight. Based upon the weight data, the counter tends to overcount.

Mechanical findings were noted in at least 6% of the devices used in the study. Some of the mechanical findings may have contributed to FNC discrepancies.

Patient satisfaction surveys indicated that over 90% of subjects reported satisfaction with the counter device and indicated the counter device would help them avoid running out of medication.

Overall the incidence of AEs was 31%. In general, the most common AEs reported were consistent with the Ventolin HFA product label.

7.2 SAS30033

An Open-Label, Multi-Center Study to Evaluate the Performance and Patient Satisfaction of Fluticasone Propionate/Salmeterol HFA with Counter 110/21mcg in Asthma or COPD Subjects at Least 12 Years of Age

7.2.1 Conduct

SAS30033 has the same design as SB030003. Therefore, only the pertinent differences in protocols will be addressed. The first difference is that study medication in SAS30033 is fluticasone propionate/salmeterol HFA with counter 110/21mcg. As in Study SB030003, SAS30033 consisted of a 7-21 day screening period followed by the study period. For the open-label study period, subjects were instructed to take two puffs of fluticasone propionate/salmeterol with counter110/21mcg in the morning and two puffs at night. Because fluticasone propionate/salmeterol with counter 110/21mcg has 120 actuations, the duration of the open-label study period was approximately 30 days. The study commenced on May 16, 2003, and was completed on November 5, 2003.

The study population was slightly different from SB030003 in that only subjects 12 years of age and older with a history of asthma or COPD were enrolled to ensure the following [N020983\S_009\2004-12-17\clinstat\SAS30033-04protocol.pdf, p 12]:

- In subjects ≥ 12 years of age, approximately half of the subjects enrolled have asthma and the other half of the subjects have COPD
- Approximately 25% of the subjects (n=63) enrolled are ≥ 65 years of age.

Reviewer's Comment: SB030003 enrolled subjects 4 years of age and older. Because the dose of fluticasone propionate used in this study is not approved in children between 4-11 years of age, only subjects 12 years of age and older were enrolled.

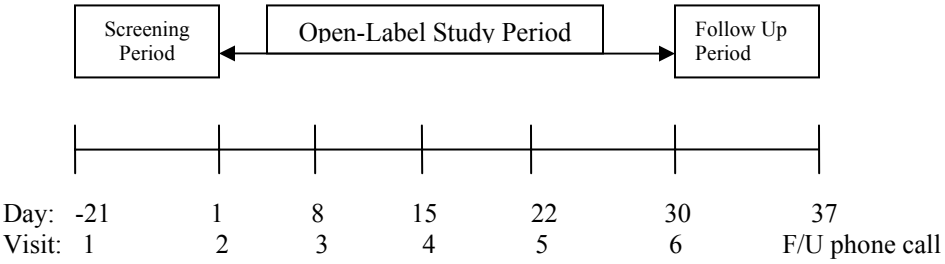
The exclusion criteria for SAS30033 were essentially the same as Study SB030003. The following is a list of inclusion criteria for Study SAS30033, which differ slightly from Study SB030003 [N020983\S_009\2004-12-17\clinstat\SAS30033-04protocol.pdf, p 19].

- Male or females ≥ 12 years of age
- Use of one of the following asthma/COPD regimens at baseline
    - Inhaled Advair Diskus 250/50 BID

- Other mid-strength ICS and a comparable dose of inhaled long-acting $beta_2$ agonist administered concurrently
- A mid-strength ICS and require short-acting $beta_2$ agonist for rescue greater than 2 times per week
- Inhaled Advair Diskus 100/50 and require short-acting $beta_2$ agonist for rescue greater than 2 times per week
- Other low-strength ICS and a comparable dose of inhaled long-acting $beta_2$ agonist administered concurrently and require a short-acting $beta_2$ agonist for rescue greater than 2 times per week.

Because this study is shorter in duration than Study SB030003, Figure 7 is included to illustrate the study schedule. Subjects in the open-label study period returned for clinic visits on Day 8 (Visit 3), 15 (Visit 4), 22 (Visit 5), and then Day 30 (Visit 6). A few days prior to Visit 6, the study center called the subject to coordinate the end of treatment visit date. A follow up phone call was made to the subject approximately one week after the final clinic visit (Visit 6) to assess for AEs. Study assessments were the same as in SB030003, except the fact that there was one less clinic visit in this study.

Figure 7 Study Schedule for SAS30033



7.2.2 Study Centers

A total of 38 investigators in the United States participated in Study SAS30033 [N020983\S_009\2004-12-17\clinstat\SAS30033-02csr.pdf, p 18].

7.2.3 Materials

The following materials were utilized in Study SAS30033:

- Fluticasone propionate/salmeterol HFA 110/21mcg
- Fluticasone propionate/salmeterol HFA with counter 110/21mcg
  - Batch numbers E03B139 and E03B470
- Ventolin HFA 90mcg provided as rescue medication.

7.2.4 Results

7.2.4.1 Subject Disposition

A total of 310 subjects were screened for Study SAS30033 and 237 were assigned to active treatment. Although four populations were specified in the protocol, this review of the study report focuses on two populations, the ITT population and completer population. The ITT population was defined as all subjects who received at least one actuation of fluticasone propionate/salmeterol HFA 110/21mcg with counter, thus the ITT Population was 237. The completer population was the Applicant's pre-specified primary population of interest and was defined as all subjects who recorded 90% of the actuations of fluticasone propionate/salmeterol HFA on the diary card. The completer population was 228 [N020983\S_009\2004-12-17\clinstat\SAS30033-02csr.pdf, p 58].

An Intent to Treat Impact Analysis Population was defined a posteriori as all subjects in the ITT population but excluding data points where values were provided after the counter reached zero, out of range data, impossible values, or significant data entry errors were noted. The ITT impact analysis population was 237, which was the same as the ITT population [N020983\S_009\2004-12-17\clinstat\SAS30033-02csr.pdf, p 58].

Of the 310 subjects screened, 237 were assigned to open label treatment. Overall, 232 (98%) of subjects assigned to open-label treatment completed the study. This number is different from the number of subjects in the pre-specified completer population, which was 228. Table 17 displays subject disposition by age strata for Study SAS30033.

Table 17 Subject Disposition by Age Strata for Study SAS30033 (ITT Population)

	Age 12-64 N=159 n(%)	**Age ≥ 65 N=78 n (%)**	**Total N=237 n(%)**
Assigned to open-label treatment	159	78	237
Completed	154 (97)	78 (100)	232 (98)
Discontinued	5 (3)	0	5 (3)
AE	1 (<1)	0	1 (<1)
Voluntary withdrawal	1 (<1)	0	1 (<1)
Protocol Violation	2 (<1)	0	2 (<1)
Exacerbation	1 (<1)	0	1 (<1)

Source [N020983\S_009\2004-12-17\clinstat\SAS30033-02csr.pdf, p 60]

Reviewer's Comment: The study was designed to enroll >25% of subjects in the ≥65 years of age range and achieved that goal.

Reviewer's Comment: The Applicant also presented subject disposition by disease – asthma and COPD. Two subjects with asthma and three subjects with COPD discontinued.

Approximately 35% of the subjects had protocol deviations during the study. The most common reason for protocol deviations was the "Other" category, which included study visits outside the

protocol-defined windows and failure to make follow-up phone calls. Additional common protocol violations included non-compliance with study procedures after enrollment [N020983\S_009\2004-12-17\clinstat\SAS30033-02csr.pdf, p62].

7.2.4.2 Demographics and Baseline Characteristics

The majority of subjects in Study SAS30033 were caucasian. The mean age was 54, with an age range of 13 to 86 years. There was a higher percentage of subjects with asthma (54%) versus COPD (46%). Table 18 displays the demographics and baseline characteristics of the study population in Study SAS30033.

Table 18 Demographics and Baseline Characteristics in Study SAS30033 ITT Population

	Age 12-64 N=159 n(%)	**Age ≥ 65 N=78 n (%)**	**Total N=237 n(%)**
Gender			
Male	65 (41)	32 (41)	97 (41)
Female	94 (59)	46 (59)	140 (59)
Age			
Mean (Range)	46 (13-64)	71 (65-86)	54 (13-86)
Race			
Caucasian	139 (87)	74 (95)	213 (90)
Black	11 (7)	1 (1)	12 (5)
Hispanic	4 (3)	3 (4)	7 (3)
Asian	3 (2)	0	3 (2)
Other	2 (1)	0	2 (1)
Disease group			
Asthma	101 (64)	27 (35)	128 (54)
COPD	58 (36)	51 (65)	109 (46)

Source [N020983\S_009\2004-12-17\clinstat\SAS30033-02csr.pdf, p 63]

Reviewer's Comment: The Applicant also presented the baseline characteristics and demographics for the completer population. No significant differences in baseline characteristics were noted between the ITT population and completer population.

Reviewer's Comment: The Applicant presented the baseline characteristics by disease strata. As expected the asthma population was younger (mean age 46 years) than the COPD population (mean age 63 years). Approximately half of the COPD population was ≥ 65 years of age.

7.2.4.3 Study Endpoints

No efficacy parameters were measured during this open-label single arm study. The Applicant evaluated the pre-specified study endpoints using the ITT population and the completer population. As stated above, the completer population was defined as subjects who recorded at least 90% (or 108) of the actuations of fluticasone propionate/salmeterol HFA on the diary card. The data will be presented for the completer population. Significant differences in the ITT

population compared to the completer population will be noted. There were 228 subjects in the completer population compared to 237 in the ITT population.

The Applicant presented the diary card data in quartiles to determine concordance with the dose counter over the life of the device. Overall, of the 13,294 subject reported handlings, only 86 handlings had missing diary data. Table 19 displays the patient handlings and actuations for Study SAS30033. A "handling" is defined as each row of diary data recorded during each dosing from the device. Therefore in this table, for each counter reading quartile, there would typically be approximately 15 handlings (30 actuations) per subject.

Table 19 Diary Card Summary of Reported Handlings and Actuations Study SAS30033 Completer Population

	Counter Reading 91-120	Counter Reading 61-90	Counter Reading 31-60	Counter Reading 0-30	Total
Number of subjects	228	228	228	228	228
Total subject reported handlings[1]	3415	3422	3428	3014	13,294
Number of handlings with missing diary data	15	12	21	25	86
Number of handlings with no missing diary data	3400	3410	3407	2989	13,208
Total number of subject reported actuations[2]	6806	6823	6814	5964	26,411

1 A "handling" is each row of the diary data recorded during each dosing from the device. For each counter reading category, there would typically be approximately 15 handlings (30 actuations) per subject.
2 Total reported actuations is based upon non-missing handlings and is the sum of PUFFNUM from diary data
Source: [N020983\S_009\2004-12-17\clinstat\SAS30033-02csr.pdf, p 71]

Reviewer's Comment: For the ITT population, the number of handlings without missing diary data was 13,521 and the total number of subject reported actuations was 27,037.

Of the 13,208 recorded device handlings without missing diary data, 248 discrepancies were noted, which is a diary card discrepancy rate of 1.88 discrepancies per 100 handlings. The majority of the discrepancies noted were count not fire (CNF), followed by count unknown fire (CUF), count up unknown fire (CUUF), and fire not count (FNC). Table 20 displays the diary card discrepancies for the completer population.

Table 20 Diary Card Discrepancies and Discrepancy Rate Study SAS30033 Completer Population					
	Counter Reading 91-120	**Counter Reading 61-90**	**Counter Reading 31-60**	**Counter Reading 0-30**	**Total**
Number of subjects	228	228	228	228	228
Number of handlings with no missing diary data	3400	3410	3407	2989	13,208
Total number of diary card discrepancies	75	69	71	29	248
Count not fire (CNF)	29	34	25	15	105
Count unknown fire (CUF)	19	11	21	6	57
Count up unknown fire (CUUF)	14	14	18	4	52
Fire not count (FNC)	13	10	7	4	34
Diary card discrepancy rate per 100 handlings	2.21	2.02	2.08	0.97	1.88
Count not fire (CNF)	0.85	1.00	0.73	0.50	0.79
Count unknown fire (CUF)	0.56	0.32	0.62	0.20	0.43
Count up unknown fire (CUUF)	0.41	0.41	0.53	0.13	0.39
Fire not count (FNC)	0.38	0.29	0.21	0.13	0.26

Source: [N020983\S_009\2004-12-17\clinstat\SAS30033-02csr.pdf, p 73]

Reviewer's Comment: For the ITT population, the overall diary card discrepancy rate was 1.87 discrepancies per 100 handlings. The CNF, CUF, CUUF, FNC discrepancy rates were 0.79, 0.43, 0.39, and 0.26 discrepancies per 100 handlings, respectively, which are essentially the same as the rates for the completer population.

The most common discrepancy was count not fire, which occurred at a rate of 0.79 discrepancies per 100 handlings. The count not fire rate was greater than fire not count rate throughout the life of the device. The overall fire not count rate was 0.26 discrepancies per 100 handlings. There does not appear to be any significant pattern of discrepancies based on the quartiles of life of the counter.

Reviewer's Comment: As stated in the Agency's Guidance to Industry: Integration of Dose-Counting Mechanisms into MDI Drug Products, if a low frequency of error is unavoidable, the device should be designed to specifically avoid undercounting (i.e. avoid FNC). The counter has the least number of FNC discrepancies.

The discrepancy rate per actuations is shown below in Table 21. The most common discrepancy was count not fire, which was 0.40 discrepancies per 100 actuations over the life of the device. The overall fire not count discrepancy rate was 0.13 discrepancies per 100 reported actuations.

Table 21 Diary Card Actuations and Discrepancy Rate per Actuations Study SAS30033 Completer Population					
	Counter Reading 91-120	**Counter Reading 61-90**	**Counter Reading 31-60**	**Counter Reading 0-30**	**Total**
Number of subjects	228	228	228	228	228
Number of handlings with no missing diary data	3400	3410	3407	2989	13,208
Total number of subject reported actuations	6806	6823	6814	5964	26,411
Total number of diary card discrepancies	75	69	71	29	248
Count not fire (CNF)	29	34	25	15	105
Count unknown fire (CUF)	19	11	21	6	57
Count up unknown fire (CUUF)	14	14	18	4	52
Fire not count (FNC)	13	10	7	4	34
Diary card discrepancy rate per 100 actuations	1.10	1.01	1.04	0.49	0.94
Count not fire (CNF)	0.43	0.50	0.37	0.25	0.40
Count unknown fire (CUF)	0.28	0.16	0.31	0.10	0.22
Count up unknown fire (CUUF)	0.21	0.21	0.26	0.07	0.20
Fire not count (FNC)	0.19	0.15	0.10	0.07	0.13

Source: [N020983\S_009\2004-12-17\clinstat\SAS300333-02csr.pdf, p 75]

Reviewer's Comment: As expected, since one handling typically represents two actuations, the discrepancy rate per 100 actuations was approximately half of the discrepancy rate per handling.

Reviewer's Comment: For the ITT population, the overall diary card discrepancy rate per 100 actuations was 0.94. The CNF, CUF, CUUF, FNC rate were 0.40, 0.21, 0.20, and 0.13 per 100 actuations, respectively.

For the completer population, 58% of subjects did not have discrepancies between diary recordings and the counter readings. Approximately 20% of subjects noted one discrepancy, 5% noted two discrepancies, 8% noted three discrepancies, and 4% noted four discrepancies. More than four discrepancies were noted, but in less than 6% of subjects. One subject reported 18 discrepancies (Subject 462) [N020983\S_009\2004-12-17\clinstat\SAS300333-02csr.pdf, p 77].

Of the 248 noted discrepancies between diary cards and counter readings, the primary discrepancy size was one or two actuations as shown below in Table 22. Discrepancy sizes between the diary card and counter readings ranged from 1 actuation to 200 actuations.

Table 22 Diary Card Summary of Discrepancy Size Study SAS30033 Completer Population					
	Count Not Fire (CNF)	**Count Unknown Fire (CUF)**	**Count Up Unknown Fire (CUUF)**	**Fire Not Count (FNC)**	**All Categories**
Total discrepancies	105	57	52	34	248
Discrepancy Size, n (%)					
1	73 (70)	17 (30)	1 (2)	6 (18)	97 (39)
2	19 (18)	35 (61)	37 (71)	28 (82)	119 (48)
3	5 (5)	3 (5)	3 (6)	0	11 (4)
4	2 (2)	1 (2)	1 (2)	0	4 (2)
5	2 (2)	0	2 (4)	0	4 (2)
>5	4 (4)	1 (2)	8 (15)	0	13 (5)

Source: [N020983\S_009\2004-12-17\clinstat\SAS30033-02csr.pdf, p 78]

Reviewer's Comment: There were 253 total discrepancies in the ITT Population, 40% of which were one actuation and 47% were two actuations. Six percent of the discrepancies were >5 actuations. The patient diaries of the subjects who had discrepancy size of more than 5 actuations were reviewed. Many of the discrepancies were due to data entry errors or diary card recording errors. Therefore, the discrepancy size (or miscounts) is likely overestimated by this patient handling study.

The Applicant determined the discrepancy size per 120 reported actuations as follows. The diary card discrepancy sizes were summed and multiplied by 100 then divided by the total reported actuations for nonmissing data. This value was then multiplied by 1.2 to report the data based on a 120 actuation canister size. Discrepancy size per 120 actuations is shown below in Table 23.

Table 23 Diary Card Summary Discrepancy Size per 120 Actuations[1] Study SAS30033 Completer Population			
	Number of Discrepancies	**Sum of Discrepancy Sizes**	**Discrepancy Size per 120 Reported Actuations[1]**
All Discrepancies	248	1180	5.36
Count Not Fire	105	493	2.24
Count Unknown Fire	57	120	0.55
Count Up Unknown Fire	52	505	2.29
Fire Not Count	34	62	0.28

Source: [N020983\S_009\2004-12-17\clinstat\SAS30033-02csr.pdf, p 80]

1 The discrepancy size per 120 reported actuations is the sum of the diary card discrepancy sizes multiplied by 100 then divided by the total reported actuations for nonmissing data. This value was then multiplied by 1.2 to report the data based on a recommended 120 actuation canister size.

Reviewer's Comment: For the ITT population, the overall discrepancy size per 120 actuations was 5.32. CNF, CUF, CUUF, FNC discrepancy sizes were 2.20, 0.59, 2.25, and 0.28, respectively.

Count up unknown fire contributed the highest discrepancy sizes. Fire not count contributed the least to the size of discrepancy. The overall discrepancy size per 120 actuations for the completer population was 5.36 actuations.

The Applicant performed "ITT Impact Analyses" post hoc. The population included all subjects in the ITT Population but excluded or corrected data points where values were provided after the counter reached zero, out of range data, impossible values, or significant data entry errors were noted. The Applicant deleted 9 data rows and corrected 5 data rows for the ITT impact analyses [N020983\S_009\2004-12-17\clinstat\SAS30033-02csr.pdf, p 82-83].
Reviewer's Comment: The post hoc ITT impact analyses should be interpreted with caution. Therefore, the entirety of the data is not presented here. Overall, there was a discrepancy rate of 0.94 discrepancies per 100 actuations, which was the same as in the ITT population. Count not fire was the most common discrepancy with fire not counts the least common discrepancy. The discrepancy size per 120 actuations was 2.94 actuations, of which 1.09 were CNF and 0.26 were FNC. This is significantly different from the ITT population.

Subgroup analyses by age, disease, and gender were performed. For age subgroup analyses, age groups were 12-64 years and ≥65 years. Table 24 displays the data from the Applicant's subgroup analyses.

Discrepancies occurred at a slightly higher rate in the ≥65 years of age range than in the 12-64 years of age. Discrepancy size was higher in the ≥65 years age group with 9.67 actuations per 120 actuations compared to 3.23 actuations per 120 actuations in the 12-64 years age group. There were fewer subjects with COPD, but a similar rate of discrepancies in the COPD and asthma population. However, the discrepancy size was higher in the COPD population at 9.12 actuations per 120 actuation compared to 2.21 actuations per 120 actuations in the asthma population. There were no significant differences in discrepancy rates or sizes based upon gender.

Table 24 Subgroup Analyses for Completer Population – Study SAS30033

	Completer Population	
Number of Subjects	N = 228	
Total Number of Diary Card Discrepancies (rate per 100 actuations), size per 120 actuations	248 (0.94) 5.36	
Count Not Fire (CNF)	105 (0.40) 2.24	
Count Unknown Fire (CUF)	57 (0.22) 0.55	
Count Up Unknown Fire (CUUF)	52 (0.20) 2.29	
Fire Not Count (FNC)	34 (0.13) 0.28	
	Age	
	Age 12-64 Years	Age ≥65 Years
Number of Subjects	N = 152	N = 76
Total Number of Diary Card Discrepancies (rate per 100 actuations), size per 120 actuations	124(0.70) 3.23	124 (1.42) 9.67
Count Not Fire (CNF)	44 (0.25) 1.09	61 (0.70) 4.57
Count Unknown Fire (CUF)	29 (0.16) 0.46	28 (0.32) 0.71
Count Up Unknown Fire (CUUF)	38 (0.21) 1.53	14 (0.16) 3.85
Fire Not Count (FNC)	13 (0.07) 0.16	21 (0.24) 0.54
	Disease	
	Asthma	COPD
Number of Subjects	N = 124	N = 104
Total Number of Diary Card Discrepancies (rate per 100 actuations), size per 120 actuations	132 (0.92) 2.21	116 (0.96) 9.12
Count Not Fire (CNF)	57 (0.40) 0.74	48 (0.40) 4.02
Count Unknown Fire (CUF)	29 (0.20) 0.42	28 (0.23) 0.70
Count Up Unknown Fire (CUUF)	34 (0.24) 0.89	18 (0.15) 3.98
Fire Not Count (FNC)	12 (0.08) 0.17	22 (0.18) 0.42
	Gender	
	Females	Males
Number of Subjects	N = 134	N = 94
Total Number of Diary Card Discrepancies (rate per 100 actuations), size per 120 actuations	147 (0.95) 5.30	101 (0.93) 5.45
Count Not Fire (CNF)	70 (0.45) 2.33	35 (0.32) 2.11
Count Unknown Fire (CUF)	30 (0.19) 0.56	27 (0.25) 0.53
Count Up Unknown Fire (CUUF)	33 (0.21) 2.24	19 (0.17) 2.38
Fire Not Count (FNC)	14 (0.09) 0.18	20 (0.18) 0.43

Source: [N020983\S_009\2004-12-17\clinstat\SAS30033-02csr.pdf, p 85]

Reviewer's Comment: The results of the subgroup analyses for the ITT population were very similar and are shown below in Table 25.

Table 25 Subgroup Analyses for ITT Population – Study SAS30033

	ITT Population	
Number of Subjects	N = 237	
Total Number of Diary Card Discrepancies (rate per 100 actuations), size per 120 actuations	253 (0.94) 5.32	
Count Not Fire (CNF)	107 (0.40) 2.20	
Count Unknown Fire (CUF)	58 (0.21) 0.59	
Count Up Unknown Fire (CUUF)	53 (0.20) 2.25	
Fire Not Count (FNC)	35 (0.13) 0.28	
	Age	
	Age 12-64 Years	Age ≥65 Years
Number of Subjects	N = 159	N = 78
Total Number of Diary Card Discrepancies (rate per 100 actuations), size per 120 actuations	129(0.71) 3.28	124 (1.39) 9.44
Count Not Fire (CNF)	46 (0.25) 1.07	61 (0.68) 4.47
Count Unknown Fire (CUF)	30 (0.17) 0.54	28 (0.31) 0.70
Count Up Unknown Fire (CUUF)	39 (0.22) 1.51	14 (0.16) 3.76
Fire Not Count (FNC)	14 (0.08) 0.16	21 (0.23) 0.52
	Disease	
	Asthma	COPD
Number of Subjects	N = 128	N = 109
Total Number of Diary Card Discrepancies (rate per 100 actuations), size per 120 actuations	132 (0.90) 2.17	121 (0.98) 9.02
Count Not Fire (CNF)	57 (0.39) 0.73	50 (0.40) 3.93
Count Unknown Fire (CUF)	29 (0.20) 0.41	29 (0.23) 0.80
Count Up Unknown Fire (CUUF)	34 (0.23) 0.87	19 (0.15) 3.88
Fire Not Count (FNC)	12 (0.08) 0.16	23 (0.19) 0.42
	Gender	
	Females	Males
Number of Subjects	N = 140	N = 97
Total Number of Diary Card Discrepancies (rate per 100 actuations), size per 120 actuations	149 (0.94) 5.19	104 (0.93) 5.49
Count Not Fire (CNF)	71 (0.45) 2.28	36 (0.32) 2.07
Count Unknown Fire (CUF)	30 (0.19) 0.54	28 (0.25) 0.66
Count Up Unknown Fire (CUUF)	33 (0.21) 2.18	20 (0.18) 2.34
Fire Not Count (FNC)	15 (0.09) 0.18	20 (0.18) 0.42

Source: [N020983\S_009\2004-12-17\clinstat\SAS30033-02csr.pdf, p 87]

Diary card comments were not common during the study (~2% of handlings). Comments prior to handling included: dropped canister, accidental actuation, misfire, or forgot dose. Comments after use included: dropped canister, child playing with canister, no medication delivered, or forgot/missed dose [N020983\S_009\2004-12-17\clinstat\SAS30033-02csr.pdf, p 90].

The Applicant weighed the canisters prior to shipping to the study site and on return of the canister from the study site. Two batches of study medication were used for this study: E03B139 and E03B470. For the completer population, the mean weight prior to shipping was 33.4g. The mean weight upon return was 25.1g. The mean difference was 8.4g. The expected mean number

of actuations used based upon canister weight was 114 with a range of 111-118 actuations. The mean number of actuations based upon subject reported actuations was 120-121 [N020983\S_009\2004-12-17\clinstat\SAS30033-02csr.pdf, p 90-91].
Reviewer's Comment: For the ITT population, the expected mean number of actuations based upon weight was 113 with a range of 109-116. The mean number of actuations based upon subject reported actuations was 119 and 118, respectively.

As in Study SB030003, any MDI with counter device experiencing a "major failure" was investigated. Of the 237 devices used by subjects in the ITT population, 38 devices met the criteria for investigation and 19 devices were analyzed. Nineteen were not analyzed for the following reasons: evidence of misuse (4), device not returned (4), database entry errors (8), and diary errors (3). Of the 19 analyzed, 9 had some mechanical finding, 4 of which were deemed a potential cause of the discrepancy. Mechanical defect categories included: (b) (4)

[N020983\S_009\2004-12-17\clinstat\SAS30033-02csr.pdf, p 94-95].
Reviewer's Comment: At least 4% of the devices used in the study had mechanical findings. At least 2% of the devices used in the study had mechanical findings as a potential cause of discrepancies.

Patient satisfaction surveys were collected by the Applicant. Subject satisfaction was based on a five point scale, with higher scores indicating increased satisfaction with therapy. At baseline, most subjects reported anxiety about not knowing how much medication remained. Subjects reported a variety of methods to determine how much medication remained. Over 90% of subjects reported satisfaction with the counter device and indicated the counter device would help them avoid running out of medication.
Reviewer's Comment: The patient satisfaction survey is not a validated patient reported outcome instrument.

7.2.4.4 Safety

Safety data is presented for the ITT population. Approximately 76% of subjects were exposed to fluticasone/salmeterol HFA with counter for >28 days. The mean number of days of exposure was 29 days. The mean number of days of exposure was similar in both age groups and in both disease groups [N020983\S_009\2004-12-17\clinstat\SAS30033-02csr.pdf, p 104-105].

There were no deaths reported in this study. Three SAES were reported during the study. One occurred during the treatment phase (ankle fracture) and the other two occurred during the screening phase (COPD exacerbation and cellulitis) [N020983\S_009\2004-12-17\clinstat\SAS30033-02csr.pdf, p 111].

One subject was withdrawn from the study for an upper respiratory tract infection and COPD exacerbation [N020983\S_009\2004-12-17\clinstat\SAS30033-02csr.pdf, p 112].

A total of 62 subjects (26%) reported at least one AE during the treatment period. Common adverse events noted in Study SAS30033 are shown below in Table 26. Pharyngolaryngeal pain and headaches were the most common AEs reported.

Table 26 Adverse Events Occurring at an Incidence ≥3% During the Treatment Period by Age Strata in Study SAS30033 ITT Population

	Age 12-64 N=159 n(%)	Age ≥ 65 N=78 n (%)	Total N=237 n(%)
Any Event	43 (27)	19 (24)	62 (26)
Respiratory, thoracic disorders			
Any Event	9 (6)	5 (6)	14 (6)
Pharyngolaryngeal pain	4 (3)	2 (3)	6 (3)
Nervous system disorders			
Any Event	8 (5)	7 (9)	15 (6)
Headache	5 (3)	3 (4)	8 (3)

Source: [N020983\S_009\2004-12-17\clinstat\SAS30033-02csr.pdf, p 106]

Three subjects experienced a COPD (1) or asthma (2) exacerbation during the study. The reported causes of the exacerbations were unknown and allergy. The subject with the COPD exacerbation was withdrawn from the study, while the other two subjects remained in the study, which was a protocol violation [N020983\S_009\2004-12-17\clinstat\SAS30033-02csr.pdf, p 112].

7.2.5 Conclusions

In Study SAS30033, 237 subjects were assigned to open-label treatment with fluticasone proprionate/salmeterol HFA MDI with counter following a screening period. The majority of subjects 228 recorded at least 108 actuations (>90% of 120 actuations) on the diary card. This population was defined as the completer population.

Overall, there was a high level of concordance between the recorded actuations in the diary and indicated by the counter. Based upon diary recordings in the completer population, 248 discrepancies were noted with the counter out of a total 26,411 reported actuations. The discrepancy rate was 0.94 discrepancies per 100 actuations. The discrepancy size was 5.36 actuations per 120 actuations. The most common discrepancies were CNF or overcounts. In the ITT population, there was an overall discrepancy rate of 0.94 per 100 actuations and a discrepancy size of 5.32 actuations per 120 actuations.

Of particular interest were the FNC discrepancies or undercounts. In the ITT population, the FNC rate was 0.13 discrepancies per 100 actuations and the FNC discrepancy size was 0.28 actuations per 120 actuations.

Returned cannisters were evaluated for the number of actuations based upon weight. Based upon the canister weight data, there appear to have been more CNFs or overcounts.

Mechanical findings were noted in 4% of the devices. Some of the mechanical findings may have accounted for some FNC discrepancies.

Patient satisfaction surveys indicated that over 90% of subjects reported satisfaction with the counter device and indicated the counter device would help them avoid running out of medication.

Overall the incidence of AEs was 26%. The most common AEs reported were headaches and pharyngolaryngeal pain.

8 LABELING REVIEW

The Applicant submitted proposed labeling for Ventolin HFA, which included a significant number of proposed changes. The proposed label was reviewed. As expected some of the proposed changes address the counter. Many of the changes are simply a rearrangement of information in the current product label and are acceptable. However, the major issue with the proposed product label is addressing the issue of appropriate priming of Ventolin HFA, which affects many sections of the product label. The recommended labeling changes are too extensive to list in this section. A revised product label containing recommended changes will be conveyed to the Applicant.

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/s/

Sally Seymour
4/4/05 04:59:02 PM
MEDICAL OFFICER

Eugene Sullivan
4/4/05 05:28:20 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-983/S009

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW #2

1 ORGANIZATION	2 NDA NUMBER
HFD-570 DPADP	20-983

3 NAME AND ADDRESS OF APPLICANT (City and State)	4 AF NUMBER	5 SUPPLEMENT(S) NUMBER / DATE
GlaxoSmithKline (GSK) Research Triangle Park, NC 27709		SCM-009 17-DEC-2004 (assigned 01-JAN-2005)

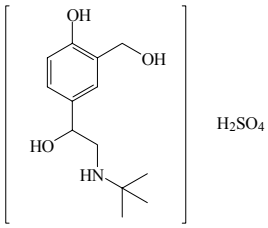
6 NAME OF DRUG	7 NONPROPRIETARY NAME
Ventolin® HFA Inhalation Aerosol	albuterol sulfate HFA inhalation aerosol

8 SUPPLEMENT PROVIDES FOR:	9 AMENDMENT(S), REPORT(S), ETC
registration of the Ventolin HFA MDI Counter. This is a prior-approval supplement.	SCM-009 C 21-DEC-2004 SCM-009* 23-FEB-2005 (assigned 01-MAR-2005) SCM-009* 25-MAR-2005 (assigned 31-MAR-2005) *subjects of CR#2

10 PHARMACOLOGICAL CATEGORY	11 HOW DISPENSED	12 RELATED IND/NDA/DMF
Beta-agonist for treatment or prevention of bronchospasm in patients 4 yrs. and older with reversible obstructive airway disease and for prevention of exercise-induced bronchospasm	RX X OTC __	DMF (b) DMF (b)

13 DOSAGE FORM(S)	14 POTENCY
inhalation aerosol	108 mcg albuterol sulfate (90 mcg base)/act from actuator (120 mcg of albuterol sulfate/act from valve), 75 mg suspension/act

15 CHEMICAL NAME AND STRUCTURE



Albuterol Sulfate, α^1-[(*tert*-Butylamino)methyl]-4-hydroxy-*m*-xylene- α, α'-diol sulfate (2:1) (salt); Molecular Formula: $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$; Molecular Weight: 576.72 (base 239.32)

16 RECORDS AND REPORTS
CURRENT YES X NO _
REVIEWED YES _ NO X

COMMENTS: The supplement is a PAS. See minutes of the 26-OCT-2004, telecon for dialog regarding submission. The supplement has been submitted in the CTD format and contains clinical patient-use study results (consult forwarded to the medical officer, S. Seymour, MD).

cc:
Orig. NDA #20-983
HFD-570/div. File
HFD-570/CBertha 4/05/05
HFD-570/RLostritto
HFD-570/SSeymour
HFD-570/ESullivan
HFD-570/AGreen
R/D Init. by:_____
F/T by: C. Bertha/4/05/05
doc # 05-02-23_rev.doc

18 CONCLUSIONS AND RECOMMENDATIONS: The supplement is recommended for **approval (AP)** from the CMC perspective. I concurred with the labeling revisions from the clinical team sent to the applicant on 05-APR-2005 that relate to the counter and priming. The action letter should remind GSK of their agreement to perform the study outlined in comment 1 of the 23-MAR-2005, telephone facsimile.

19 REVIEWER NAME	20 SIGNATURE	21 DATE COMPLETED
Craig M. Bertha, Ph.D.		05-APR-2005

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_✓___ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(4) Draft Labeling

____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry-20-983/S009

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/s/

Craig Bertha
4/13/05 09:59:14 AM
CHEMIST

Richard Lostritto
4/14/05 03:29:58 PM
CHEMIST

CHEMIST'S REVIEW #1

1. ORGANIZATION	2. NDA NUMBER
HFD-570 DPDP	20-983

3. NAME AND ADDRESS OF APPLICANT (City and State)	4. AF NUMBER	5. SUPPLEMENT(S) NUMBER / DATE
GlaxoSmithKline (GSK) Research Triangle Park, NC 27709		SCM-009 17-DEC-2004 (assigned 03-JAN-2005)

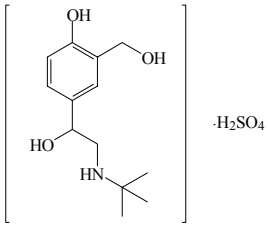
6. NAME OF DRUG	7. NONPROPRIETARY NAME
Ventolin® HFA Inhalation Aerosol	albuterol sulfate HFA inhalation aerosol

8. SUPPLEMENT PROVIDES FOR:	9. AMENDMENT(S), REPORT(S), ETC.
registration of the Ventolin HFA MDI Counter. This is a prior-approval supplement.	SCM-009 C 21-DEC-2004

10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED	12. RELATED IND/NDA/DMF
Beta-agonist for treatment or prevention of bronchospasm in patients 4 yrs. and older with reversible obstructive airway disease and for prevention of exercise-induced bronchospasm	RX X OTC _	

13. DOSAGE FORM(S)	14. POTENCY
inhalation aerosol	108 mcg albuterol sulfate (90 mcg base)/act from actuator (120 mcg of albuterol sulfate/act from valve), 75 mg suspension/act

15. CHEMICAL NAME AND STRUCTURE



Albuterol Sulfate, "[1]-[(*tert*-Butylamino)methyl]-4-hydroxy-*m*-xylene-","'-diol sulfate (2:1) (salt); Molecular Formula: $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$; Molecular Weight: 576.72 (base 239.32)

16. RECORDS AND REPORTS
CURRENT YES X NO _
REVIEWED YES _ NO X

COMMENTS: The applicant has submitted the supplement as a PAS. See minutes of the 26-OCT-2004, telecon for latest dialog between Agency and firm regarding the submission of this supplement. The supplement has been submitted in the CTD formation and contains clinical patient-use study results. A consult has been forwarded to the clinical team for the latter.

cc:
Orig. NDA #20-983
HFD-570/div. File
HFD-570/CBertha 1/18/05
HFD-570/RLostitto
HFD-570/SBarnes
HFD-570/AGreen
R/D Init. by:_____
F/T by: C. Bertha/1/18/05
doc # 04-12-17_rev.doc

18. CONCLUSIONS AND RECOMMENDATIONS: The supplement is considered approvable (AE). The PM should forward the comments in the draft letter to the applicant in a discipline review (DR) letter.

19. REVIEWER NAME	20. SIGNATURE	21. DATE COMPLETED
Craig M. Bertha, Ph.D.		18-JAN-2005

__40____ Page (s) Withheld

_✓___ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(4) Draft Labeling

____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry-20-983/S009

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/s/

Craig Bertha
1/21/05 06:06:46 AM
CHEMIST
signing for R. Lostritto, Team Leader

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-983/S009

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

MEMORANDUM

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

DATE: April 13, 2005

SUBJECT: **Labeling Revisions**
NDA 20-983/S-009, Ventolin HFA Inhalation Aerosol

The following labeling revision requests were conveyed to Mr. Robert Bohinski, Associate Director, Respiratory, US Regulatory Affairs, at GlaxoSmithKline, via voicemail and email:

1. Line 500: Change (b) (4) to "cap from the mouthpiece of the actuator (the strap on the cap will stay attached to the actuator),".

2. Line 501: Change (b) (4) to "...face, shaking..."

3. The word ("or") is missing from the Word version of the carton. Item 10, currently includes the following text: (b) (4) Change this to: "Contact your pharmacist for a refill of your prescription or consult...".

Akilah Green, Regulatory Project Manager

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/s/

Akilah Green
4/13/05 03:56:55 PM
CSO

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

FACSIMILE TRANSMITTAL SHEET

Date: April 5, 2005

To: Robert Bohinski **Assistant Director, Regulatory Affairs**	**From:** Akilah Green Regulatory Project Manager
Company: GSK	Division of Pulmonary and Allergy Drug Products
Fax number: 919-315-4364	**Fax number:** 301-827-1271
Phone number: 919-483-5636	**Phone number:** 301-827-5585

Subject: NDA 20-983/S-009 Labeling comments

Total no. of pages including cover: 24

Comments:

Document to be mailed: YES X NO

NDA 20-983/S-009

We have reviewed your draft labeling for the Package Insert and Patient Instructions for Use dated December 17, 2004, for NDA 20-983/S-009. Attached are our proposed labeling changes. We have accepted your proposed changes as well as made additional edits.

If you have any questions, you may contact Ms. Akilah Green, Regulatory Project Manager, at 301-827-5585.

___21___ Page (s) Withheld

____ Trade Secret / Confidential (b4)

__✓__ Draft Labeling (b4)

____ Draft Labeling (b5)

____ Deliberative Process (b5)

Withheld Track Number: Administrative-20-983/S009

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/s/

Akilah Green
4/5/05 01:42:03 PM
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

Date: March 23, 2005

To: Robert Bohinski **Assistant Director, Regulatory Affairs**	**From:** Akilah Green Regulatory Project Manager
Company: GSK	Division of Pulmonary and Allergy Drug Products
Fax number: 919-315-4364	**Fax number:** 301-827-1271
Phone number: 919-483-5636	**Phone number:** 301-827-5585

Subject: NDA 20-983/S-009 CMC comments fax

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES X NO

NDA 20-983/S-009

Your submission dated, December 17, 2004, to NDA 20-983, is currently under review and we have the following request:

1. (b) (5) [redacted]

2. Be aware that Drug Master File (b) (4) [redacted] (February, 22, 2005, amendment) was reviewed and found to be inadequate to support your supplemental application. A deficiency letter dated March 15, 2005, has been forwarded to the holder. As part of your response, include confirmation that the DMF holder has responded to the deficiency and include the date of their response. You are encouraged to contact the DMF holder to discuss the nature of the deficiency and work with them to address this so that a positive action can be taken on your supplement.

If you have any questions, you may contact Ms. Akilah Green, Regulatory Project Manager, at 301-827-5585.

Drafted by:	Green/March 21, 2005
Initialed:	Barnes/March 22, 2005
	Bertha/March 22, 2005
	Lostritto/March 22, 2005
Finalized:	Green/March 23, 2005

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/s/

Akilah Green
3/23/05 02:57:12 PM
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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	REQUEST FOR CONSULTATION

TO: *(Division/Office)* Eugene Sullivan, MD, Dep. Div. Dir (HFD-570)	FROM: Craig M. Bertha, Ph.D./HFD-570

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
3/16/05		20-983	SCS-009 BC (see EDR)	2/23/05 (electronic)

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Ventolin® HFA (albuterol sulfate inhalation aerosol)	3	S	3/13/05 (1 week prior to PDUFA)

NAME OF FIRM: GlaxoSmithKline, Inc.

REASON FOR REQUEST

I. GENERAL

□ NEW PROTOCOL
□ PROGRESS REPORT
□ NEW CORRESPONDENCE
□ DRUG ADVERTISING
□ ADVERSE REACTION REPORT
□ MANUFACTURING CHANGE/ADDITION
□ MEETING PLANNED BY
□ PRE-NDA MEETING
□ END OF PHASE II MEETING
□ RESUBMISSION
□ SAFETY/EFFICACY
□ PAPER NDA
□ CONTROL SUPPLEMENT
□ RESPONSE TO DEFICIENCY LETTER
□ FINAL PRINTED LABELING
□ LABELING REVISION
□ ORIGINAL NEW CORRESPONDENCE
□ FORMULATIVE REVIEW
☒ OTHER *(Specify below)*

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER	☐ CHEMISTRY ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER

III. BIOPHARMACEUTICS

☐ DISSOLUTION
☐ BIOAVAILABLITY STUDIES
☐ PHASE IV STUDIES
☐ DEFICIENCY LETTER RESPONSE
☐ PROTOCOL-BIOPHARMACEUTICS
☐ *IN-VIVO* WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
☐ CASE REPORTS OF SPECIFIC REACTIONS *(List below)*
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ SUMMARY OF ADVERSE EXPERIENCE
☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please evaluate the Safety Assessment included in the response to comment 6.

cc: Orig. NDA # 20-983
HFD-570/Div. File
HFD-570/RLostritto/CBertha
HFD-570/ESullivan/SSeymour
HFD-570/SBarnes/AGreen

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SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Craig Bertha

3/16/05 06:38:05 AM

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

FACSIMILE TRANSMITTAL SHEET

DATE: March 15, 2005

To: Robert Bohinski Associate Director, Respiratory, US Regulatory Affairs	Akilah Green **From:** Regulatory Project Manager
Company: GlaxoSmithKline	Division of Pulmonary and Allergy Drug Products
Fax number: 919-315-8319	**Fax number:** 301-827-1271
Phone number: 919-483-5636	**Phone number:** 301-827-5585

Subject: NDA 20-983, S-009 Clinical Information Request

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES xNO

Your submission dated, December 17, 2004, to NDA# 20-983, is currently under review and we have the following request:

> Provide additional information regarding diary card discrepancy sizes >5 actuations for Studies SB030003 and SAS30033 for both the completer population and ITT population. Include the subject number, discrepancy size, discrepancy category, and any additional relevant information regarding discrepancies >5 actuations. If the requested information is in the above submission, provide the location of the requested information.

If there are any questions, please contact Akilah Green, Project Manager, at 301-827-5585.

Drafted by: Seymour/March 14, 2005
Initialed: Barnes/March 15, 2005
Sullivan/March 14, 2005
Finalized: Green/March 15, 2005

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/s/

Akilah Green
3/15/05 03:37:33 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-983 **DISCIPLINE REVIEW LETTER**

Glaxo SmithKline
PO Box 13398
Five Moore Drive
Research Triangle Park, North Carolina 27709-3398

Attention: Robert J. Bohinski
Associate Director, Respiratory US Regulatory Affairs

Dear Dr. Abdullah:

Please refer to your December 17, 2004, supplemental new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ventolin HFA (albuterol sulfate) Inhalation Aerosol.

Our review of the Chemistry, Manufacturing and Controls data in your submission is complete, and we have identified the following deficiencies. In order to be useful during this review cycle, we need to receive your complete response by February 25, 2005:

1. Clarify whether or not the (b) (4) equipment checks *each* counter for (b) (4) (p. 6, P4). And verify that this testing by the (b) (4) equipment is distinct from the joint strength and appearance tests which are done on a sample of units from a manufacturing/packaging run.

2. Provide the sampling frequencies for both the counter joint strength and appearance tests that are applied in-process during the manufacture of the Ventolin HFA MDI Counter.

3. Tighten the acceptance criteria of the critical Count Accuracy test (p. 7 of P7) such that the count is within ± 2 of the expected count. Your Count Accuracy data (section 10.7 on p. 80 of P10) indicates a much higher level of accuracy than you are requiring upon acceptance of the counters.

4. The Major category acceptable quality level of (b) (4) for acceptance of counters with damage in the joint region or with numbers that can not be read may result in drug product with counters that do not perform in patient's hands. Revise the AQL to the pass/fail level or provide additional information that would assure that the 100% checks of function and counts performed by the (b) (4) (p. 6 of P4) would be able to reject such counters that were (b) (4) canisters.

5. Provide data and a justification for the increase in the allowance of 2 – 3 fold in the peak intensities of new peaks in blank or control samples obtained during the performance of actuator extractables profiling testing by FTIR. Address any change in (b) (4) quality that may have occurred since the original method was approved.

6. Provide any additional data or the results of studies for Ventolin HFA or Ventolin HFA MDI Counter related to the phenomenon of 2-5 fold increase above target delivery of the drug substance in the first few actuations for product that has not been used for an extended time after manufacture prior to first use. The results of your priming study on the 8 month old product presented on p. 3 of P10 concerns us since patients that fail to prime the unit using the 4 actuation recommendation could receive an initial overdose of the drug substance 3 fold higher (540 mcg) than the expected dose of 180 mcg. The relationship, if any, to the installation of the counter should also be addressed in your response.

7. We acknowledge your proposal to modify the labeling to inform patients to reprime the device (4 sprays) after the unit is accidentally dropped.

8. Provide data (e.g., from (b) (4)) that demonstrate improvement in the counter accuracy and reliability that has resulted from the various improvements made to the prototype device (i.e., (b) (4)

9. Identify the counter acceptance tests that will be used routinely to detect any recurrence of the potential mechanical defect of (b) (4).

10. Drug Master File (b) (4) was reviewed and was found to be inadequate to support your supplemental application. A deficiency letter has been forwarded to the holder. As part of your response, include confirmation that the DMF holder has responded to all of their deficiencies and include the date of their response.

11. Drug Master File (b) (4) was reviewed and was found to be inadequate to support your supplemental application. A deficiency letter has been forwarded to the holder. As part of your response, include confirmation that the DMF holder has responded to all of their deficiencies and include the date of their response.

12. Provide confirmation that the (b) (4) counter actuators used in the patient use study drug had racks that were manufactured to the same dimensions and tolerances as the (b) (4) counter actuator that was used in the *in vitro* comparability and drug product characterization studies.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Akilah Green, Regulatory Project Manager, at 301-827-5585.

Sincerely,

Richard Lostitto, Ph.D.
Chemistry Team Leader
Division of Pulmonary and Allergy Drug Products, HFD-570
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Richard Lostritto

1/28/05 04:03:02 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-983/S-009 **PRIOR APPROVAL SUPPLEMENT**

GlaxoSmithKline
P.O. Box 13398
Five Moore Drive
Research Triangle Park
North Carolina 27709-3398

Attention: Robert J. Bohinski
Associate Director, Respiratory US Regulatory Affairs

Dear Mr. Bohinski:

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

Name of Drug Product:	Ventolin (albuterol sulfate) HFA inhalation Aerosol
NDA Number:	20-983
Supplement number:	S-009
Review Priority Classification:	Standard (S)
Date of supplement:	December 17, 2004
Date of receipt:	December 20, 2004

This supplemental application provides for the registration of the MDI counter.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 18, 2005, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be April 20, 2005.

Send all electronic or mixed electronic and paper submission to the Central Document Room at the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

If your submission only contains paper, send it to the following address:

U.S. Postal Service/Courier/Overnight Mail:
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Drug Products, HFD-570
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Ms. Akilah Green, Regulatory Project Manager, at (301) 827-5585.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Supervisory CSO
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Akilah Green
1/18/05 04:29:25 PM
Signed for Sandy Barnes

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**

TO: *(Division/Office)* Eugene Sullivan, MD, Dep. Div. Dir (HFD-570)	FROM: Craig M. Bertha, Ph.D./HFD-570

DATE 1/10/05	IND NO.	NDA NO. 20-983	TYPE OF DOCUMENT SCS-009	DATE OF DOCUMENT 12/17/04
NAME OF DRUG Ventolin® HFA (albuterol sulfate inhalation aerosol)		PRIORITY CONSIDERATION 3	CLASSIFICATION OF DRUG S	DESIRED COMPLETION DATE 4/01/05

NAME OF FIRM: GlaxoSmithKline, Inc.

REASON FOR REQUEST

I. GENERAL

9 NEW PROTOCOL
9 PROGRESS REPORT
9 NEW CORRESPONDENCE
9 DRUG ADVERTISING
9 ADVERSE REACTION REPORT
9 MANUFACTURING CHANGE/ADDITION
9 MEETING PLANNED BY

9 PRE-NDA MEETING
9 END OF PHASE II MEETING
9 RESUBMISSION
9 SAFETY/EFFICACY
9 PAPER NDA
9 CONTROL SUPPLEMENT

9 RESPONSE TO DEFICIENCY LETTER
9 FINAL PRINTED LABELING
9 LABELING REVISION
9 ORIGINAL NEW CORRESPONDENCE
9 FORMULATIVE REVIEW
: OTHER *(Specify below)*

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
9 TYPE A OR B NDA REVIEW 9 END OF PHASE II MEETING 9 CONTROLLED STUDIES 9 PROTOCOL REVIEW 9 OTHER	9 CHEMISTRY 9 PHARMACOLOGY 9 BIOPHARMACEUTICS 9 OTHER

III. BIOPHARMACEUTICS

9 DISSOLUTION
9 BIOAVAILABLITY STUDIES
9 PHASE IV STUDIES

9 DEFICIENCY LETTER RESPONSE
9 PROTOCOL-BIOPHARMACEUTICS
9 *IN-VIVO* WAIVER REQUEST

IV. DRUG EXPERIENCE

9 PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
9 DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
9 CASE REPORTS OF SPECIFIC REACTIONS *(List below)*
9 COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

9 REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
9 SUMMARY OF ADVERSE EXPERIENCE
9 POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

9 CLINICAL 9 PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please evaluate the clinical data and information (i.e., patient handling studies, post-marketing experience, labeling, etc.) included in the supplement (CTD modules 1, 2 and 5) to support the approval of the Ventolin HFA product with an incorporated dose counter in the actuator. The network path for the electronic submission is **\\Cdsesub1\n20983\S_009\2004-12-17**.

cc: Orig. NDA # 20-983
HFD-570/Div. File
HFD-570/GPoochikian/CBertha
HFD-570/ESullivan/SSeymour
HFD-570/SBarnes/AGreen

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/s/

Richard Lostritto

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