CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 76-130

***Name*:** Albuterol Extended-release Tablets, 4 mg and 8 mg

***Sponsor*:** Sidmak Laboratories, Inc.

***Approval Date*:** September 26, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-130

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-130

APPROVAL LETTER

ANDA 76-130

SEP 26 2002

Sidmak Laboratories, Inc.
Attention: Deborah L. Pakay
17 West Street
P.O. Box 371
East Hanover, NJ 07936

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated March 2, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Albuterol Extended-release Tablets, 4 mg and 8 mg.

Reference is also made to your amendments dated July 19, and August 3, 2001; and May 21, May 31, June 21, and September 23, 2002. We also refer to your communications dated May 15 and June 22, 2001, pertaining to patent issues related to the approval of the drug product.

The listed drug product (RLD) referenced in your application, Volmax Extended-release Tablets of Muro Pharmaceutical, Inc., is subject to periods of patent protection. As noted in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book", these patents are scheduled to expire on June 14, 2005 (U.S. Patent Nos. 4,751,071 (the '071 patent) and 4,851,229 (the '229 patent) and October 11, 2005 (U.S. Patent No. 4,777,049 (the '049 patent). Your application contains patent certifications to each of these patents under Section 505(j)(2)(A)(vii)(IV) of the Act stating that the patents are invalid and/or will not be infringed by the manufacture, use, or sale of your drug product. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an action is brought against Sidmak Laboratories Inc. (Sidmak) for infringement of one or more of the listed patents that are the subject of the "paragraph IV certifications". Such action must be brought against Sidmak before the expiration of forty-five (45) days from the date the notice you provided to the NDA/patent holder(s) under paragraph (2)(B)(i) was received.

You have notified FDA that Sidmak complied with the requirements of Section 505(j)(2)(B) of the Act, and that no action for patent infringement was brought against Sidmak within the statutory forty-five day period.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Albuterol Extended-release Tablets, 4 mg and 8 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug, Volmax® Extended-release Tablets, 4 mg and 8 mg, of Muro Pharmaceutical Inc. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application. The "interim" dissolution specifications for both strengths of the drug are as follows:

Time (Hr)	% Dissolution
2	[redacted]
4	[redacted]
6	[redacted]
8	NLT [redacted]

The in vitro dissolution testing should be conducted in 900 mL of de-ionized water using USP apparatus 2 (paddle) at 50 rpm.

The "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data for the first three production size batches. Data should be submitted as a Special Supplement - Changes Being Effected when there are no revisions to the "interim" specifications or when the final specifications are tighter than the "interim" specifications. In all other instances, the information should be submitted in the form of a Prior Approval Supplement.

Furthermore, we note that Sidmak was the first applicant to submit a substantially complete ANDA containing "paragraph IV certifications" to the listed patents for this drug product.

Therefore, with this approval, Sidmak is eligible for 180-days of market exclusivity for each strength as provided for under the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments) in Section 505(j)(5)(B)(iv) of the Act. Such exclusivity will begin to run on the date Sidmak begins commercial marketing.

With respect to the "first commercial marketing" trigger for the commencement of exclusivity, please refer to 21 CFR 314.107 (c)(4). The agency expects that you will begin commercial marketing of this drug product in a prompt manner. Please submit correspondence to your application stating the date you commenced commercial marketing of the product.

If you have any questions concerning the effective date of approval of an ANDA and the agency's elimination of the requirement that an ANDA applicant successfully defend a patent infringement suit to be eligible for 180-days of marketing exclusivity, please refer to the interim rule published in the November 5, 1998 Federal Register (Volume 63, No. 214, 59710).

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 9/26/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-130
Division File
Field Copy
HFD-610/R. West
HFD-210/B. Poole
HFD-330
HFD-205
HFD-92

Endorsements:
HFD-645/D.Maldonado/ DMR 8/16/02.
HFD-645/B.Arnwine/8/15/02 (31 comments) 8/19/02
HFD-617/N.Park/ NPark 8/19/02
HFD-613/A.Payne/ APayne 8/18/02 no changes in labeling
HFD-613/J.Grace/ Grace for J. Grace 8/19/02

Robert Lupfest
9/26/2002

v:/firmsnz/sidmak/ltrs&rev/76130d.ap
F/T by rad8/16/02

APPROVAL
PACT

cmc satisfactory.
Lloyd Y. Tsuyuki
8/21/02.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-130

LABELING

SEP 30 2002

APPROVED

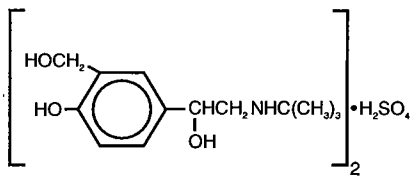
080645

P08-0645

ALBUTEROL EXTENDED-RELEASE TABLETS

Rx only Rev. 1/02

DESCRIPTION: Albuterol extended-release tablets contain albuterol sulfate, the racemic form of albuterol and a relatively selective beta$_2$-adrenergic bronchodilator, in an extended-release formulation. 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 structural formula:



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

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

Each tablet for oral administration contains 4 mg or 8 mg of albuterol as 4.8 mg or 9.6 mg, respectively, of albuterol sulfate in a cellulosic material that serves as a diffusion-release membrane. In addition each tablet contains the following inactive ingredients: Calcium sulfate, carnauba wax, ethylcellulose, ferric oxide black, hydroxypropyl methylcellulose, ink-thinner XI, lactose monohydrate, magnesium stearate, polyethylene glycol, propylene glycol, shellac, stearic acid, titanium dioxide, triacetin, D&C Yellow #10, and FD&C Blue #1.

CLINICAL PHARMACOLOGY: *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 indicates that there is a population of beta$_2$-receptors in the human heart existing in a concentration between 10% and 50%. The precise function of these receptors has not been established. (See Warnings).

The pharmacologic effects of beta-adrenergic agonist drugs, including albuterol, are at least in part attributable to stimulation through beta-adrenergic receptors on intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3′, 5′-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

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.

Albuterol is longer acting than isoproterenol in most patients by any route of administration because it is not a substrate for the cellular uptake processes for catecholamines nor for catechol-O-methyl transferase.

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 were administered concurrently. The clinical significance of these findings is unknown.

Pharmacokinetics and Disposition: In a single-dose study comparing one 8 mg albuterol extended-release tablet with two 4 mg immediate-release albuterol tablets, USP in 17 normal adult volunteers, the extent of availability of albuterol extended-release tablets was shown to be about 80% of albuterol tablets, USP with or without food. In addition, lower mean peak plasma concentration and longer time to reach the peak level were observed with albuterol extended-release tablets as compared with albuterol tablets, USP. The single-dose study results also showed that food decreases the rate of absorption of albuterol from albuterol extended-release tablets without altering the extent of bioavailability. In addition, the study indicated that food causes a more gradual increase in the fraction of the available dose absorbed from the extended-release formulation as compared with the fasting condition.

In another single-dose study in adults, 8 mg and 4 mg albuterol extended-release tablets were shown to deliver dose-proportional plasma concentrations in the fasting state. Definitive studies for the effect of food on 4 mg albuterol extended-release tablets have not been conducted. However, since food lowers the rate of absorption of 8 mg albuterol extended-release tablets, it is expected that food reduces the rate of absorption of 4 mg albuterol extended-release tablets also.

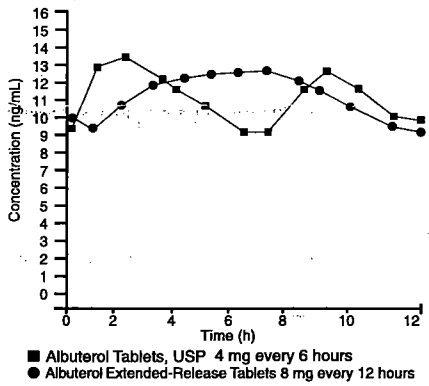
Albuterol extended-release tablets have been formulated to provide duration of action of up to 12 hours. In an 8-day, multiple-dose, crossover study, 15 normal adult male volunteers were given 8 mg albuterol extended-release tablets every 12 hours or 4 mg albuterol tablets, USP every 6 hours. Each dose of albuterol extended-release tablets and the corresponding doses of albuterol tablets, USP were administered in the postprandial state. Steady-state plasma concentrations were reached within 2 days for both formulations. Fluctuations (C_{max}-C_{min}/$C_{average}$) in plasma concentrations were similar for albuterol extended-release tablets administered at 12-hour intervals and albuterol tablets, USP administered every 6 hours. In addition, the relative bioavailability of albuterol extended-release tablets was approximately 100% of the immediate-release tablet at steady state. A summary of these results is shown in the following table:

Mean Values at Steady State

	C_{max} (ng/mL)	C_{min} (ng/mL)	T_{max} (h)	$T_{1/2}$ (h)	AUC (ng-h/mL)
Albuterol Extended-Release Tablets	13.7	8.1	6.0	9.3	134
Albuterol Tablets, USP	13.9	8.1	2.6	7.2	132

The mean plasma albuterol concentration versus time data at steady state after the administration of albuterol extended-release tablets 8 mg every 12 hours are displayed in the following graph:

Mean Plasma Albuterol Concentration at Day 8



Pharmacokinetic studies of 4- and 8-mg albuterol extended-release tablets have not been conducted in pediatric patients. Bioavailability of 4- and 8-mg albuterol extended-release tablets in pediatric patients relative to 2- and 4-mg immediate release albuterol has been extrapolated from adult studies showing comparability at steady-state dosing and reduced bioavailability after single dose administration.

INDICATIONS AND USAGE: Albuterol extended-release tablets are indicated for the relief of bronchospasm in adults and children 6 years of age and older with reversible obstructive airway disease.

CONTRAINDICATIONS: Albuterol extended-release tablets are contraindicated in patients with a history of hypersensitivity to albuterol or any of its components.

WARNINGS: Immediate hypersensitivity reactions may occur after administration of albuterol, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, and oropharyngeal edema.

Cardiovascular Effects: Albuterol extended-release tablets, like all other beta-adrenergic agonists, can produce a clinically significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of albuterol extended-release tablets 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, albuterol extended-release tablets, 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 albuterol extended-release tablets than usual, 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.

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.

Paradoxical Bronchospasm: Albuterol extended-release tablets can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs, albuterol extended-release tablets should be discontinued immediately and alternative therapy instituted.

Rarely, erythema multiforme and Stevens-Johnson syndrome have been associated with the administration of oral albuterol in children.

PRECAUTIONS:

General: Albuterol, as with all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; 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 and could be expected to occur in some patients after use of any beta-adrenergic bronchodilator.

In controlled clinical trials in adults, patients treated with albuterol extended-release tablets had increases in selected serum chemistry values and decreases in selected hematologic values. Increases in SGPT were more frequent among patients treated with albuterol extended-release tablets (12 of 247 patients, 4.9%) than among the theophylline (6 of 188 patients, 3.2%) and placebo (1 of 138 patients, 0.7%) groups. Increases in serum glucose concentration were also more frequent among patients treated with albuterol extended-release tablets (23 of 234 patients, 9.8%) than among theophylline (11 of 173 patients, 6.45%) and placebo (3 of 129 patients, 2.3%) groups. Increases in SGOT were also more frequent among patients treated with albuterol extended-release tablets (10 of 248 patients, 4%) and theophylline (5 of 193, 2.6%) than among patients treated with placebo. Decreases in white blood cell counts were more frequent in patients treated with albuterol extended-release tablets (10 of 247 patients, 4%) compared with patients receiving theophylline (2 of 185 patients, 1.1%) and patients receiving placebo (1 of 141 patients, 0.7%). Decreases in hemoglobin and hematocrit were more frequent in patients receiving albuterol extended-release tablets (16 of 228 patients, 7.0%, and 17 of 230 patients, 7.4%, respectively) than in patients receiving theophylline (5 of 171 patients, 2.9%, and 9 of 173 patients, 5.2%, respectively) and patients receiving placebo (5 of 129 patients, 3.9%, and 3 of 132 patients, 2.3%, respectively). The clinical significance of these results is unknown.

Large doses of intravenous albuterol have been reported to aggravate pre-existing 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:

Albuterol extended-release tablets must be swallowed whole with the aid of liquids. DO NOT CHEW OR CRUSH THESE TABLETS.

The action of albuterol extended-release tablets should last up to 12 hours or longer. Albuterol extended-release tablets should not be used more frequently than recommended. Do not increase the dose or frequency of albuterol extended-release tablets without consulting your physician. If you find that treatment with albuterol extended-release tablets 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 albuterol extended-release tablets, other inhaled drugs and asthma medications should be taken only as directed by your physician. Common adverse effects include palpitations, chest pain, rapid heart rate, tremor or nervousness. If you are pregnant or nursing, contact your physician about use of albuterol extended-release tablets. Effective and safe use of albuterol extended-release tablets includes an understanding of the way that it should be administered.

Drug Interactions: The concomitant use of albuterol extended-release tablets and other oral sympathomimetic agents is not recommended since such combined use may lead to deleterious cardiovascular effects. This recommendation does not preclude the judicious use of an aerosol bronchodilator of the adrenergic stimulant type in patients receiving albuterol extended-release tablets. Such concomitant use, however, should be individualized and not given on a routine basis. If regular coadministration is required, then alternative therapy should be considered.

Monoamine Oxidase Inhibitors or Tricyclic Antidepressants: Albuterol 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 albuterol extended-release tablets, but may produce severe bronchospasm in asthmatic patients. 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 could be considered, although they should be administered with caution.

Diuretics: The ECG changes and/or hypokalemia that may result from the administration of non potassium-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 non potassium-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 significant dose-related increase in the incidence of benign leiomyomas of the mesovarium at dietary doses of 2.0, 10, and 50 mg/kg, (approximately 1/2, 3, and 15 times, respectively, the maximum recommended daily oral dose for adults on a mg/m² basis, or, approximately 2/5, 2, and 10 times, respectively, the maximum recommended daily oral dose for children on a mg/m² 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 65 times the maximum recommended daily oral dose for adults on a mg/m² basis, or, approximately 50 times the maximum recommended daily oral dose for children on a mg/m² basis). In a 22 month study in the Golden hamster, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of 50 mg/kg, (approximately 7 times the maximum recommended daily oral dose for adults and children on a mg/m² basis).

Albuterol sulfate was not mutagenic in the Ames test with or without metabolic activation using tester strains *S. typhimurium* TA 1537, TA 1538, and TA98 or *E. coli* WP2, WP2uvrA, and WP67. No forward mutation was seen in yeast strain *S. cerevisiae* S9 nor any mitotic gene conversion in yeast strain *S. cerevisiae* JD1 with or without metabolic activation. Fluctuation assays in *S. typhimurium* TA98 and *E. coli* WP2, both with metabolic activation, were negative. Albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or in an AH1 strain mouse micronucleus assay at intraperitoneal doses of up to 200 mg/kg.

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses up to 50 mg/kg, (approximately 15 times the maximum recommended daily oral dose for adults on a mg/m² basis).

Pregnancy: Teratogenic Effects: Pregnancy Category C: Albuterol Sulfate has been shown to be teratogenic in mice. A study in CD-1 mice at subcutaneous (SC) doses of 0.025, 0.25, and 2.5 mg/kg, (approximately 3/1000, 3/100, and 3/10 times the maximum recommended daily oral dose for adults on a mg/m² basis), showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg. The drug did not induce cleft palate formation at the lowest dose, 0.025 mg/kg. Cleft palate also occurred in 22 of 72 (30.5%) fetuses of females treated with 2.5 mg/kg, of isoproterenol (positive control) subcutaneously (approximately 3/10 times the maximum recommended daily oral dose for adults on a mg/m² basis). A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7/19 fetuses (37%) when albuterol sulfate was administered orally at a 50 mg/kg dose, (approximately 25 times the maximum recommended daily oral dose for adults on a mg/m² basis).

There are no adequate and well-controlled studies in pregnant women. Albuterol 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 rarely 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.

Labor and Delivery: Because of the potential for beta-agonist interference with uterine contractility, use of albuterol extended-release tablets for relief of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

Tocolysis: Albuterol has not been approved for the management of pre-term labor. The benefit:risk ratio when albuterol is administered for tocolysis has not been established. Serious adverse reactions, including pulmonary edema, have been reported during or following treatment of premature labor with $beta_2$-agonists, including albuterol.

Nursing Mothers: It is not known whether albuterol is excreted in human milk. Because of the potential for tumorigenicity shown for albuterol in animal studies, 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.

Pediatric Use: The safety and effectiveness of albuterol extended-release tablets have been established in pediatric patients 6 years of age or older. Use of albuterol extended-release tablets in these age groups is supported by evidence from adequate and well-controlled studies of albuterol extended-release tablets in adults; the likelihood that the disease course, pathophysiology, and the drug's effect in pediatric and adult patients are substantially similar; the established safety and effectiveness of immediate release albuterol tablets in pediatric patients 6 years of age and older; and clinical trials that support the safety of albuterol extended-release tablets in pediatric patients over 6 years of age. The recommended dose of albuterol extended-release tablets for the pediatric population is based upon the recommended pediatric dosing of immediate-release albuterol tablets and pharmacokinetic studies in adults showing comparable bioavailability at steadystate dosing and reduced bioavailability after single dose administration. Safety and effectiveness in pediatric patients below 6 years of age have not been established.

ADVERSE REACTIONS: The adverse reactions to albuterol are similar in nature to reactions to other sympathomimetic agents. The most frequent adverse reactions to albuterol are nervousness, tremor, headache, tachycardia, and palpitations. Less frequent adverse reactions are muscle cramps, insomnia, nausea, weakness, dizziness, drowsiness, flushing, restlessness, irritability, chest discomfort, and difficulty in micturition.

Rare cases of urticaria, angioedema, rash, bronchospasm, and oropharyngeal edema have been reported after the use of albuterol.

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

In controlled clinical trials of adult patients conducted in the United States, the following incidence of adverse events was reported:

	Albuterol Extended-Release Tablets	Theophylline	Other Beta-agonists	Placebo
Event (*n*=330)	(*n*=197)	(*n*=20)	(*n*=178)	
Tremor	24.2%	6.1%	35.0%	1.1%
Headache	18.8%	26.9%	35.0%	20.8%
Nervousness	8.5%	5.1%	10.0%	2.8%
Nausea/Vomiting	4.2%	19.8%	5.0%	3.9%
Tachycardia	2.7%	0.5%	5.0%	0%
Muscle Cramps	2.7%	0.5%	5.0%	0.6%
Palpitations	2.4%	0.5%	0%	1.1%
Insomnia	2.4%	6.1%	0%	1.7%
Dizziness	1.5%	2.0%	0%	5.1%
Somnolence	0.3%	1.0%	0%	0.6%

A trend was observed among patients treated with albuterol extended-release tablets toward increasing frequency of muscle cramps with increasing patient age (12-20 years, 1.2%; 21-30 years, 2.6%; 31-40 years, 6.9%; 41-50 years, 6.9%), compared with no such events in the placebo group. Also observed was an increasing frequency of tremor with increasing patient age (12-20 years, 29.4%; 21-30 years, 29.9%; 31-40 years, 27.6%; 41-50 years, 37.9%), compared to 2.9% or less in the placebo group.

The reactions are generally transient in nature, and it is usually not necessary to discontinue treatment with albuterol extended-release tablets.

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 per minute, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia. Hypokalemia may also occur. As with all sympathomimetic aerosol medications, cardiac arrest and even death may be associated with abuse of albuterol extended-release tablets.

Treatment consists of discontinuation of albuterol extended-release tablets 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 albuterol extended-release tablets.

The oral median lethal dose of albuterol sulfate in mice is greater than 2000 mg/kg, (approximately 250 times the maximum recommended daily oral dose for adults on a mg/m² basis, or, approximately 200 times the maximum recommended daily oral dose for children on a mg/m² basis). In mature rats, the subcutaneous median lethal dose of albuterol sulfate is approximately 450 mg/kg (approximately 110 times the maximum recommended daily oral dose for adults on a mg/m² basis, or, approximately 90 times the maximum recommended daily oral dose for children on a mg/m² basis). In small young rats, the subcutaneous median lethal dose is approximately 2000 mg/kg, (approximately 500 times the maximum recommended daily oral dose for adults on a mg/m² basis, or, approximately 400 times the maximum recommended daily oral dose for children on a mg/m² basis).

DOSAGE AND ADMINISTRATION: The following dosages of albuterol extended-release tablets are expressed in terms of albuterol base:

Usual Dosage:

Adults and Children over 12 years of age: The usual recommended dosage for adults and pediatric patients over 12 years of age is 8 mg every 12 hours. In some patients, 4 mg every 12 hours may be sufficient.

Children 6 to 12 years of age: The usual recommended dosage for children 6 through 12 years of age is 4 mg every 12 hours.

Dosage adjustment in Adults and Children over 12 years of age: In unusual circumstances, such as adults of low body weight, it may be desirable to use a starting dosage of 4 mg every 12 hours and progress to 8 mg every 12 hours according to response.

If control of reversible airway obstruction is not achieved with the recommended doses in patients on otherwise optimized asthma therapy, the doses may be cautiously increased stepwise under the control of the supervising physician to a maximum dose of 32 mg per day in divided doses (i.e., every 12 hours).

Dosage adjustment in Children 6 to 12 years of age: If control of reversible airway obstruction is not achieved with the recommended doses in patients on otherwise optimized asthma therapy, the doses may be cautiously increased stepwise under the control of the supervising physician to a maximum dose of 24 mg per day in divided doses (i.e., every 12 hours).

Switching from oral albuterol, USP products: Patients currently maintained on albuterol tablets, USP or albuterol sulfate syrup can be switched to albuterol extended-release tablets. For example, the administration of one 4 mg albuterol extended-release tablet every 12 hours is comparable to one 2 mg albuterol tablet, USP every 6 hours. Multiples of this regimen up to the maximum recommended daily dose also apply.

Albuterol extended-release tablets must be swallowed whole with the aid of liquids. **DO NOT CHEW OR CRUSH THESE TABLETS.**

HOW SUPPLIED: Albuterol Extended-Release Tablets, equivalent to 4 mg and 8 mg of Albuterol:

4 mg - Green, round, coated tablets in bottles of 100 and 500. Printed SL on one side and 45 on the other side in black ink.

8 mg - Green, round, coated tablets in bottles of 100 and 500. Printed SL on one side and 46 on the other side in black ink.

Dispense in a well-closed, light-resistant container as defined in the USP. Replace cap securely after each opening. Store at controlled room temperature 15°-30°C (59°-86°F).

Manufactured by:
SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

P08-0645 Rev. 1/02
c/n

NDC 50111-645-01

Albuterol Extended-Release Tablets

(oral) 4 mg*

Rx only

100 Tablets

Sidmak LABORATORIES, INC.

*Each extended-release tablet contains 4.8 mg of albuterol sulfate equivalent to 4 mg albuterol tablets.

Dispense in a well-closed, light-resistant container as defined in the USP. Replace cap securely after each opening.

Store at controlled room temperature 15°-30°C (59°-86°F).

USUAL DOSAGE: See package insert.

Tablets must be swallowed whole with the aid of liquids.

Do not chew or crush.

Control No.:

Exp. Date: SEP 30 2002

Rev. 1/02

APPROVED

SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

3 50111-645-01 1

NDC 50111-645-02

Albuterol Extended-Release Tablets

(oral) 4 mg*

Rx only

500 Tablets

Sidmak LABORATORIES, INC.

*Each extended-release tablet contains 4.8 mg of albuterol sulfate equivalent to 4 mg albuterol tablets.

Dispense in a well-closed, light-resistant container as defined in the USP. Replace cap securely after each opening.

Store at controlled room temperature 15°-30°C (59°-86°F).

USUAL DOSAGE: See package insert.

Tablets must be swallowed whole with the aid of liquids.

Do not chew or crush. SEP 30 2002

Control No.:

Exp. Date:

Rev. 1/02 APPROVED

SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

3 50111-645-02 8

NDC 50111-646-01

Albuterol Extended-Release Tablets

(oral) 8 mg*

Rx only

100 Tablets

Sidmak LABORATORIES, INC.

*Each extended-release tablet contains 9.6 mg of albuterol sulfate equivalent to 8 mg albuterol tablets.
Dispense in a well-closed, light-resistant container as defined in the USP. Replace cap securely after each opening.
Store at controlled room temperature 15°-30°C (59°-86°F).
USUAL DOSAGE: See package insert.
Tablets must be swallowed whole with the aid of liquids.
Do not chew or crush.

SEP 30 2002

Control No.:
Exp. Date:
Rev. 1/02

APPROVED

SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

N 3 50111-646-01 8

NDC 50111-646-02

Albuterol Extended-Release Tablets

(oral) 8 mg*

Rx only

500 Tablets

Sidmak LABORATORIES, INC.

*Each extended-release tablet contains 9.6 mg of albuterol sulfate equivalent to 8 mg albuterol tablets.
Dispense in a well-closed, light-resistant container as defined in the USP. Replace cap securely after each opening.
Store at controlled room temperature 15°-30°C (59°-86°F).
USUAL DOSAGE: See package insert.
Tablets must be swallowed whole with the aid of liquids.
Do not chew or crush.

SEP 30 2002

Control No.:
Exp. Date:
Rev. 1/02

APPROVED

SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

N 3 50111-646-02 5

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-130

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING #1 (first generic)
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **76-130** Date of Submission: March 2, 2001
Applicant's Name: Sidmak Laboratories, Inc.
Established Name: **Albuterol Extended-release Tablets, 4 mg and 8 mg**

Labeling Deficiencies:

1. GENERAL COMMENT: Please revise all labels and labeling to read "Albuterol Extended-release Tablets " rather than Albuterol Sulfate Extended-release Tablets.
2. CONTAINER (4 mg and 8 mg) 100s and 500s
   a. Please increase the prominence of " do not chew or crush".
   b. Revise each strength and the each tablet contain statement as follows:
      "(oral) 4 mg*.
      *Each extended-release tablet contains 4.8 mg of albuterol sulfate equivalent to 4 mg albuterol tablets.
3. [redacted] See comments under GENERAL COMMENTS and CONTAINER.
4. INSERT
   a. GENERAL COMMENT – Revise "[redacted] tablets" to read " Albuterol tablets, USP" throughout the insert.
   b. DESCRIPTION – revise "[redacted] ' to read "structural formula".
   c. HOW SUPPLIED - You may delete reference to the Ventolin trademark information.

Please revise your labels and labeling, as instructed above, and submit 12 copies of final printed labels and labeling.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes - http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):Do you have 12 Final Printed Labels and Labeling? Yes No If no, list why:
Container Labels:
Carton Labeling:
Professional Package Insert Labeling:
Patient Package Insert Labeling:
Revisions needed post-approval:
BASIS OF APPROVAL:

Patent Data For NDA 19-604

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4851229	June 14, 2005		Composition comprising a therapeutic agent and a modulating agent	P-IV	
4751071	June 14, 2005		Composition comprising salbutamol	P-IV	
4777049	Oct 11, 2005		Constant release system with pulsed release	P-IV	

Exclusivity Data For NDA: There are no unexpired protections

Code/sup	Expiration	Use Code	Description		Labeling Impact
					SAME AS

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: VOLMAX
NDA Number: 19-604
NDA Drug Name: Albuterol sulfate extended release tablets
NDA Firm: Muro
Date of Approval of NDA Insert and supplement #: s-007 approved April 6, 99
Has this been verified by the MIS system for the NDA? No
Was this approval based upon an OGD labeling guidance? No
If yes, give date of labeling guidance:
Basis of Approval for the Container Labels: container in application

Other Comments: We believe the name should be consistent with the USP Monograph for Albuterol Tablets.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N/A
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X tabs	X ER	
Is this name different than that used in the Orange Book?	X	X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		X	
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X

Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N/A
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?	X		
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.	X		
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. Review based on the labeling of NDA 19604 Volmax (S/007, revised 4-99; approved 4/6/99). Under the PRECAUTION section (4th paragraph under the General subsection and the 1st and 2nd paragraphs under Information for Patients were deleted. Because applicant delivery system is different . The applicant product is extended release but does not leave behind an outer shall in the stool (nondeformable material). CLINCIAL PHARMACOLOGY section. Since this is a product whose bio avialablity is difficult to match I suggest that we use the phrase ———————— .

3. Storage Conditions:
   NDA - store between 2 to 30C
   ANDA –CRT 15-30 C
   USP -
4. Dispensing Recommendations:
   NDA -
   ANDA- Dispense in a well-closed, light-resistant container. Replace the cap securely after each opening.
   USP - Well-closed light-resistant container
5. Scoring:
   NDA – not scored
   ANDA – not scored
   USP -
6. Product Line:
   The innovator markets their product in HDPE bottles with CRC 100s, and 500s.
   The applicant proposes to market their product in 100s and 500s
7. The tablet/capsule imprint(ings)/embossing(s)/ debossing(s) has/have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). Yes page 1366 red volume 1.3
8. Inactive Ingredients:
   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 264(Volume 1.1 red) .
9. Bio pending.
10. Manufactured by sidmake lab
11. The naming of this product should be consistent with the USP monograph for the tablets. The name should be changed from Albuterol Sulfate ER tablets to Albuterol ER tablets, 4 mg or 8 mg *. (* equivalent to 4.8 mg of albuterol sulfate.)

Date of Review: May 21, 01 **Date of Submission: March 2, 2001**

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cc: ANDA: 76-130
DUP/DIVISION FILE
HFD-613/apayne/ gracej (no cc)
V:firmsnz/sidmak/lets&revs/76130na1.L
Review

1/02/01
1/2/2002

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number	76-130
Date of Submission	Jan. 22, 2002
Applicant	Sidmak labs.
Drug Name	Albuterol Extended-release Tablets
Strength(s)	4 mg, 8 mg

FPL Approval Summary		
Container Labels		
4 mg	100s, 500s	submitted January 22, 2002 vol. 2.1 blue
8 mg	100s, 500s	Submitted January 22, 2002 vol. 2.1 blue
Package Insert Labeling	P080645 Rev. Date Jan. 2002	Submitted January 22, 2002 vol. 2.1 blue

BASIS OF APPROVAL:

Patent Data For NDA 19-604

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4851229	June 14, 2005	------	Composition comprising a therapeutic agent and a modulating agent	P-IV	No impact
4751071	June 14, 2005	-----	Composition compring salbutamol	PIV	No impact
4777049	Oct 11, 2005	-----	Constant release system with pulsed release	P-IV	No impact

Exclusivity Data For NDA 19-604			
Code/sup	**Expiration**	**Description**	**Labeling impact**
		None	

Reference Listed Drug

RLD on the 356(h) form	Volmax® Tablets
NDA Number	19-604
RLD established name	Albuterol sulfate extended-release tablets
Firm	Muro
Currently apprvoved PI	S-007
AP Date	Nov. 20, 1997

Note: FPL approved April 6, 1999

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N/A
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X tabs	X ER	
Is this name different than that used in the Orange Book?	X	X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		X	
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N/A
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?	X		
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	

Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.	X		
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. Review based on the labeling of NDA 19604 Volmax (S/007, revised 4-99; approved 4/6/99). Under the PRECAUTION section (4th paragraph under the General subsection and the 1st and 2nd paragraphs under Information for Patients were deleted. Because applicant delivery system is different . The applicant product is extended release but does not leave behind an outer shall in the stool (nondeformable material). CLINCIAL PHARMACOLOGY section.
2. Storage Conditions:
   NDA - store between 2 to 30C
   ANDA –CRT 15-30 C
   USP -
4. Dispensing Recommendations:
   NDA -
   ANDA- Dispense in a well-closed, light-resistant container. Replace the cap securely after each opening.
   USP - Well-closed light-resistant container
5. Scoring:
   NDA – not scored
   ANDA – not scored
   USP -
6. Product Line:
   The innovator markets their product in HDPE bottles with CRC 100s, and 500s.
   The applicant proposes to market their product in 100s and 500s
7. The tablet/capsule imprint(ings)/embossing(s)/ debossing(s) has/have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). Yes page 1366 red volume 1.3
8. Inactive Ingredients:
   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 264(Volume 1.1 red) .
9. Bio pending.
10. Manufactured by sidmake lab
11. The naming of this product should be consistent with the USP monograph for the tablets. The name should be changed from Albuterol Sulfate ER tablets to Albuterol ER tablets, 4 mg or 8 mg *. (* equivalent to 4.8 mg of albuterol sulfate.)

Date of Review: **February 06, 2002**

Date of Submission: **January 22, 2002**

cc: ANDA: 76-130
DUP/DIVISION FILE
HFD-613/apayne/ gracej (no cc)
V:firmsnz/sidmak/lets&revs/76130.apL
Review

2/06/02

3/6/2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-130

CHEMISTRY REVIEWS

1. CHEMISTRY REVIEW # 1

2. ANDA # 76-130

3. NAME AND ADDRESS OF APPLICANT
Sidmak Laboratories, Inc.
Attention: Roger W. Schwede
P. O. Box 371
East Hanover, NJ 07936

4. LEGAL BASIS FOR ANDA SUBMISSION
The basis of this submission is the approved listed drug, Volmax® Tablets, 4 mg and 8 mg (NDA #19-604) manufactured by Muro Pharmaceutical Inc. There are no valid patents and exclusivities (pp 12 - 15).

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Albuterol Sulfate

8. SUPPLEMENT PROVIDE FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
March 2, 2001: Original Submission
March 5, 2001: Acceptable for Filing
June 8, 2001: Bio Review #1

10. PHARMACOLOGICAL CATEGORY
Bronchodilator

11. ℞ or OTC
℞

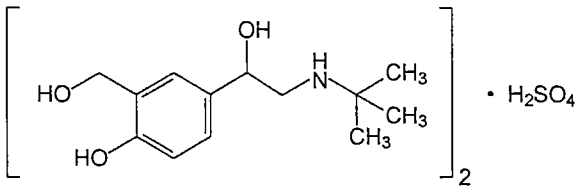
12. RELATED ANDA/DMFs

13. DOSAGE FORM
Extended Release Tablets

14. POTENCY
4 mg and 8 mg

15. CHEMICAL NAME AND STRUCTURE

Albuterol Sulfate, USP. 1,3-Benzenedimethanol, α^1-[[(1,1-dimethylethyl)amino]methyl]-4-hydroxy-, sulfate (2:1) (salt). $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$. M.W= 576.7 g/mole



16. RECORDS AND REPORTS

N/A

17. COMMENTS

See review

18. CONCLUSIONS AND RECOMMENDATIONS

Not Approvable; Minor

19. REVIEWER

Ijeoma N. Nnamani, Ph.D.

DATE COMPLETED

July 27, 2001

APPEARS THIS WAY
ON ORIGINAL

Redacted 18 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

cc: ANDA # 76-130
ANDA DUP
DIV FILE
Field Copy

Endorsements

HFD-645/INNnamani/7/27/01 Inamani 8/13/01
HFD-645/BTArnwine/8/13/01 BTArnwine 8/13/01
HFD-617/KSherrod/7/31/01 K Sherrod 8/13/01
HFD-640/FSFang/

F/T by: rad8/13/01
V: \Firmsnz\Sidmak\ltrs&rev\76130nadf

NOT APPROVABLE: MINOR

APPEARS THIS WAY
ON ORIGINAL

1. CHEMISTRY REVIEW # 3

2. ANDA # 76-130

3. NAME AND ADDRESS OF APPLICANT
Sidmak Laboratories, Inc.
Attention: Roger W. Schwede
17 West Street
P. O. Box 371
East Hanover, NJ 07936

4. LEGAL BASIS FOR ANDA SUBMISSION
The basis of this submission is the approved listed drug, Volmax® Tablets, 4 mg and 8 mg (NDA #19-604) manufactured by Muro Pharmaceutical Inc. There are no valid patents and exclusivities (pp 12 - 15).

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Albuterol Sulfate

8. SUPPLEMENT PROVIDE FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
March 2, 2001: Original Submission
March 5, 2001: Acceptable for Filing
June 8, 2001: Bio Review #1
August 9, 2001: Bio Sign Off
August 13, 2001: Chemistry Review #1
November 16, 2001: Amendment
December 3, 2001: Telephone Deficiency
December 14, 2001: Telephone Amendment
December 19, 2001: District Office Lab report
January 22, 2002: Labeling Review summary
March 5, 2002: Amendment
May 10, 2002: Bio Deficiency Letter

10. PHARMACOLOGICAL CATEGORY
Bronchodilator

11. Rx or OTC
Rx

12. RELATED ANDA/DMFs

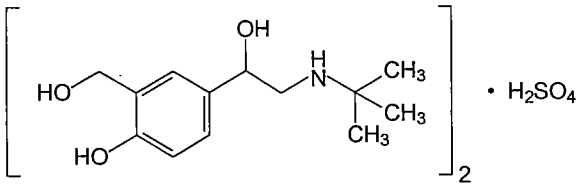
[redacted]

[redacted]

13. DOSAGE FORM
Extended Release Tablets

14. POTENCY
4 mg and 8 mg

15. CHEMICAL NAME AND STRUCTURE
Albuterol Sulfate, USP. 1,3-Benzenedimethanol, α^1-[[(1,1-dimethylethyl)amino]methyl]-4-hydroxy-, sulfate (2:1) (salt). $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$. M.W= 576.7 g/mole



16. RECORDS AND REPORTS
N/A

17. COMMENTS
See review

18. CONCLUSIONS AND RECOMMENDATIONS
Not Approvable

19. REVIEWER
Damaris Maldonado

DATE COMPLETED
May 15, 2002

APPEARS THIS WAY
ON ORIGINAL

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confidential commercial

information from

CHEMISTRY REVIEW #2

38. Chemistry comments to be provided to the applicant

ANDA: **76-130** APPLICANT: Sidmak Laboratories, Inc.

DRUG PRODUCT: Albuterol Sulfate Extended Release Tablets, 4 mg and 8 mg

The following deficiencies represent MINOR deficiencies:

The Division of Bioequivalence has requested additional information regarding your dissolution testing methodology, release and stability specifications, and time points. We await a response to the deficiency letter sent by the Bioequivalence Division on May 10th, 2002.

Sincerely yours,

5/22/02

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA # 76-130
DIV FILE
Field Copy

Endorsements

HFD-645/DMaldonado/5/15/02 DMR 5/20/02.
HFD-645/BTArnwine/5/16/02 BT Arnwine 5/21/02
HFD-617/NPark/5/15/02 NPark 5/4/02

F/T by: dss/5/17/02
V: \Firmsnz\Sidmak\ltrs&rev\76130r3

Not Approvable-Minor

APPEARS THIS WAY
ON ORIGINAL

1. CHEMISTRY REVIEW # 3

2. ANDA # 76-130

3. NAME AND ADDRESS OF APPLICANT
Sidmak Laboratories, Inc.
Attention: Deborah L. Pakay
17 West Street
P. O. Box 371
East Hanover, NJ 07936

4. LEGAL BASIS FOR ANDA SUBMISSION
The basis of this submission is the approved listed drug, Volmax® Tablets, 4 mg and 8 mg (NDA #19-604) manufactured by Muro Pharmaceutical Inc. There are no valid patents and exclusivities (pp 12 - 15).

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Albuterol Sulfate

8. SUPPLEMENT PROVIDE FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
March 2, 2001: Original Submission
March 5, 2001: Acceptable for Filing
June 8, 2001: Bio Review #1
August 9, 2001: Bio Sign Off
August 13, 2001: Chemistry Review #1
November 16, 2001: Amendment
December 3, 2001: Telephone Deficiency
December 14, 2001: Telephone Amendment
December 19, 2001: District Office Lab report
January 22, 2002: Labeling Review summary
March 5, 2002: Amendment
May 10, 2002: Bio Deficiency Letter

10. PHARMACOLOGICAL CATEGORY
Bronchodilator

11. Rx or OTC
Rx

12. RELATED ANDA/DMFs

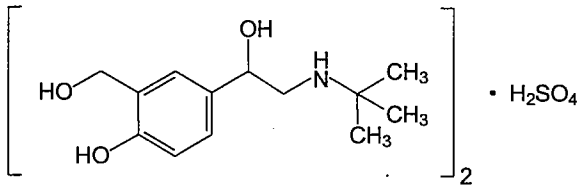
[ ]

[ ]

13. DOSAGE FORM
Extended Release Tablets

14. POTENCY
4 mg and 8 mg

15. CHEMICAL NAME AND STRUCTURE
Albuterol Sulfate, USP. 1,3-Benzenedimethanol, α^1-[[(1,1-dimethylethyl)amino]methyl]-4-hydroxy-, sulfate (2:1) (salt). $(C_{13}H_{21}NO_3)_2 \bullet H_2SO_4$. M.W= 576.7 g/mole



16. RECORDS AND REPORTS
N/A

17. COMMENTS
See review

18. CONCLUSIONS AND RECOMMENDATIONS
Approve

19. REVIEWER
Damaris Maldonado

DATE COMPLETED
August 12, 2002.

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information from

CHEMISTRY REVIEW #3

cc: ANDA # 76-130
DIV FILE
Field Copy

Endorsements

HFD-645/DMaldonado/8/14/02 8/16/02.
HFD-645/BTArnwine/8/15/02 8/19/02
HFD-617/NPark/ 8/9/02

F/T by: rad8/16/02
V: \Firmsnz\Sidmak\ltrs&rev\76130r4

Approve

APPEARS THIS WAY
ON ORIGINAL

DIVISION REVIEW SUMMARY

ANDA #: 76-130

DRUG NAME: Albuterol Sulfate

FIRM: Sidmak Laboratories, Inc.

DOSAGE FORM: Extended Release Tablets

STRENGTH: 4 mg and 8 mg

CGMP STATEMENT/EER STATUS: Acceptable on April 12, 2001.

BIO STUDY: Acceptable on July 23, 2002.

METHODS VALIDATION: Acceptable December 19, 2001.

PACKAGING: Both strengths are packaged in 100's and 500's.

STABILITY: Three months accelerated stability data for both strengths and 9 and 12 months room temperature stability data for the 8 mg and 4 mg tablets, respectively, are within specifications and support the proposed 24-month expiration period for the product.

LABELING: Acceptable. See review dated February 6, 2002.

STERILIZATION VALIDATION: N/A

ANDA BATCH: [redacted] Tablets each

SOURCE OF NDS: The firm's source of drug substance is [redacted] DMF # [redacted] was found adequate on December 27, 2001.

PROPOSED PRODUCTION BATCH: [redacted] Tablets each

RECOMMENDATION: Approve

REVIEWER: Damaris Maldonado **SIGNATURE/DATE:** DMaldonado 8/16/02.

TEAM LEADER: Brenda T. Arnwine **SIGNATURE/DATE:** BTArnwine 8/19/02

DATE: August 8, 2002

F/T by: /

V:\firmsnz\Sidmak\ltrs&rev\76130drs

APPEARS THIS WAY
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-130

BIOEQUIVALENCE REVIEWS

Albuterol Sulfate

Extended release tablets, 8-mg, 4-mg
ANDA # 76-130
Reviewer: Gur J.P. Singh
File #76130SD.301

Sidmak Labs

17West Street
East Hanover, NJ 07936
Submission Date:
March 2, 2001

Review of four bioequivalence studies and dissolution data

The sponsor has submitted single dose bioequivalence studies conducted under fasting and non-fasting conditions, and a multiple dose study on its albuterol sulfate 8-mg tablet, and a fasting study on albuterol sulfate 4-mg extended release tablet. The application also contains dissolution data for these drug products.

Reference Listed Drug

Drug Product:	Volmax® 8-mg and 4-mg extended release tablets manufactured by Muro (NDA 19604, Approval Date: December 23, 1992). Drug release from this product is controlled by osmotic pressure. The release mechanism is referred to as GITS.
Indication:	Relief of bronchospasm.
Bioavailability:	Approximately 80% following oral administration.
Metabolites:	Not reported.
Half Life:	Approximately 8-12 hours.
T_{max}:	2-4 hours
Food Effect:	Food may influence the rate of absorption.
DBE guidance:*	Not available.

* *Division of Bioequivalence*

1. Single-dose Fasting Bioequivalence Study on the 8-mg tablet (#1466)

1.1 OBJECTIVE: The purpose of this study was to establish bioequivalence of Sidmak Laboratories' albuterol sulfate **8-mg** extended release tablets to Muro's Volmax® **8-mg** extended release tablets.

1.2 STUDY SITE, INVESTIGATORS AND DATES:

Clinical study site: [redacted]

Analytical Study Site: [redacted]

Medical Director: [redacted], MD.
Analytical Director: [redacted]

Study Protocol: Protocol (#001466, June 22, 200, pp. 147-162, vol. 1.3) was approved by the [redacted] Institutional Review Board.

Dosing Dates: July 6 and 18, 2000
Analytical Dates: August 1-8, 2000

1.3 SUBJECT SELECTION:

Twenty six (26) healthy male volunteers were enrolled for this study. The mean age and weight of these volunteers were 35.4 years and 76.13 kg, respectively (vol. 1.5). Subjects who entered this study were selected based on acceptable medical history, physical examination and normal clinical laboratory tests for hematopoietic, hepatic and renal functions, and appropriate subject selection criteria outlined in the study protocol.

1.4 STUDY DESIGN: The clinical study was conducted as a single dose, randomized, two-treatment, two-period crossover evaluation with a washout period of 12 days between the two dosing days.

1.5 TREATMENTS:

A: Albuterol sulfate extended release tablets 1x8 mg, Sidmak Laboratories, Lot #: 00-0016T, Lot Size: [redacted] tablets, Content uniformity: 98.0%, Potency 98.8%

B: Volmax® extended release tablets 1x8 mg, Muro, Lot #: 10460727, Lot Size: Commercial lot, Expiry Date - December 2000, Content uniformity: 97.4%, Potency 97.4.7% .

The randomization sequence used in the study is given in the table 2 (attachment).

1.6 DOSING: After an overnight (10 hours) fast, each drug was given orally with 240 mL of water. Within one hour before and one hour after dosing, the only water supplied was with drug administration. Subjects were confined to the clinical facility until 24 hours after dosing. They returned for subsequent blood samples.

1.7 SAMPLE COLLECTION AND STORAGE:

Sample: Blood samples were collected under conditions to minimize exposure to light.

Sampling times: 0 (pre-dose) and 0.75, 1.5, 2.25, 3, 3.75, 4.5, 5.25, 6, 7, 8, 10, 12, 16, 24, 36, 48 and 60 hours post-dose (18 samples).

Sample Storage: Plasma was separated and stored at –20 ± 10 °C until analysis.

1.8 HEMODYNAMIC EVALUATIONS: Not reported.

1.9 ANALYTICAL PROCEDURE (Not to be released under FOI):

Method:

Inter-day (Within the sample analysis period, , vol. 1.13):

	Precision	Accuracy
Based on CS:	[redacted]	[redacted]
Based on QC samples:	[redacted]	[redacted]

Repeat Assays: A total of 52 samples were re-analyzed for a variety of reasons including 15 samples analyzed for anomalous values (vol. 1.13). Of these 15 samples, 11 were reported as below the limit of quantitation (same as the original-assay values) and the remaining 4 were within 5% of the original values. Furthermore, none of these data represent Cmax values. In the reviewer's opinion the impact of the use of repeat-assay values on AUC values should be negligible.

Analytical Method Deficiencies: None

1.10 PHARMACOKINETIC (PK) DATA ANALYSIS:

PK Parameters: Area under the plasma concentration vs. curve from time zero to the last quantifiable data point (AUC), $AUC_{0\text{-infinity}}$ (AUCI), C_{max}, T_{max}, elimination $t_{1/2}$ and K_{el} were computed. Parameter values were calculated for albuterol. The reviewer has verified the AUC and AUCI values. Therefore, parametric data submitted by the firm were considered to be accurate and used by the reviewer for all statistical analyses.

Statistical analyses: The reviewer performed analysis of variance (ANOVA) with subjects, period and treatment as factors, and sequence as between subject factor was applied to PK parameters. Statistical analyses of pharmacokinetic data were conducted using the t-test method to determine differences between albuterol sulfate formulations in AUC, AUCI and C_{max} at $\propto = 0.05$ and $ß = 0.20$.

1.11 RESULTS:

Clinical Study Conduct:

Number of subjects dosed: 26

Number of subjects completing the study: 24 (Subjects #7 & 25 withdrew from the study before for personal reasons).

Adverse events:	Eight (8) adverse events were reported (vol. 1.5), of which four were probably related to drug treatment (Test: Anxiety, agitation and headache, Ref.: Anxiety).
Protocol deviations:	Minor deviations related blood draw times were reported for 24 samples. In all cases nominal times were used for computation of AUCs.

PK Data:

Individual-subject plasma concentration data: Albuterol plasma concentration data are given in appendix 2 (vol. 1.5). Line graphs depicting individual-subject concentration vs. time profiles are included in the same section. The slope and intercept values for Kel determinations and time points for calculation of Kel values are listed in the same section.

Mean plasma concentration profiles: See table 1 (attachment).

AUC, AUCI and C_{max} data: See table 2 (attachment) for individual subject values, AUC/AUCI ratios and Test/Reference ratios of AUC, AUCI and C_{max}.

Bioequivalence Evaluation: Bioequivalence evaluation is based on 21 subjects' data *(Subjects 11, 19 and 21 data were not reported because subject 11 left the clinical center after his 6-hour blood draw in Period 1 but returned for period 2. His data for period 1 was incomplete. For subject 19 (Test product, period 1) and subject 21 (Reference product, Period 2) all plasma concentrations were BLQ. When questioned, the subjects admitted that they did not swallow the tablets)*

Mean parametric values and test/ref ratios: see table 3 (attachment).

90% confidence intervals: The 90% confidence intervals for AUC, AUCI and C_{max} were within the acceptable limit of 80-125% (table 3, attachment).

Sequence Effect: Not detected based on reviewer's analyses.

Deficiencies in the bioequivalence study: None

2. Non-fasting Bioavailability Study (Study #2397) on the 8-mg tablet

2.1 OBJECTIVE: The purpose of this study was to compare bioavailability of Sidmak Laboratories' albuterol sulfate **8-mg** extended release tablets to that of Muro's Volmax® **8-mg** extended release tablets under non-fasting conditions.

2.2 STUDY SITE, INVESTIGATORS AND DATES:

Clinical study site, Analytical Study Site: Same as mentioned for the fasting study.
Medical Director: [redacted], MD.
Analytical Director: [redacted]

Study Protocol: Protocol (#002397, October 18, 2000, vol. 1.3) was approved by the [redacted] Institutional Review Board.

Dosing Dates: November 3 - December 4, 2000
Analytical Dates: December 18, 2000 to January 8, 20001.

2.3 SUBJECT SELECTION:

Eighteen (18) healthy males were dosed in this study. The mean age and weight of these volunteers were 28 years and 82.3 kg, respectively. Subjects who entered this study were selected based on acceptable medical history, physical examination and normal clinical laboratory tests for hematopoietic, hepatic and renal functions, and appropriate subject selection criteria outlined in the study protocol.

2.4 STUDY DESIGN: The clinical study was conducted as a single dose, randomized, three-treatment, three-period crossover evaluation with a washout period of 14 days between the successive dosing days.

2.5 TREATMENTS:

A: Albuterol sulfate extended release tablets 1x8 mg, Sidmak Laboratories, Lot #: 00-016T, administered following an overnight fast.

B: Albuterol sulfate extended release tablets 1x8 mg, Sidmak Laboratories, Lot #: 00-016T, administered following consumption of a standardized breakfast.

C: Volmax® extended release tablets 1x8 mg, Muro, Lot #: 10460727, administered following consumption of a standardized breakfast.

The randomization code used in the study is given in the table 5 (attachment).

2.6 DOSING AND MEALS:

Each drug was given orally with 240 mL of water. The breakfast served before administration of treatments B and C included one buttered English muffin, one fried egg, one slice of American cheese, one slice of Canadian bacon, 2.5 ounces of hash brown potatoes, six fluid ounces of orange juice, eight fluid ounces of whole milk.

2.7 SAMPLE COLLECTION AND STORAGE AND HEMODYNAMIC EVALUATIONS: Same as mentioned for the fasting study.

2.8 ANALYTICAL PROCEDURE: Same as mentioned for the fasting study.

Calibration Standards' (CS) and Quality Control (QC) samples' concentrations for analysis of study samples:

CS: ———————————————————————

QC: ———————————

Specificity, Limit of Quantitation, Recovery and Stability: Same as mentioned for the fasting study. Representative chromatograms are given in volume 1.4.

Linearity: Calibration curves were linear in the range of calibration standards used (——— vol. 1.3).

Inter-day (Within the sample analysis period) Reproducibility and Accuracy :

	Precision	Accuracy
Albuterol sulfate		
Based on CS:	———	———
Based on QC samples:	———	———

(Individual run data are given in appendix 6, vol. 1.4)

Repeat Assays: A total of 8 samples were re-analyzed; 7 for loss in processing and 1 for anomalous value). The original assay value was reported for the latter.

Analytical Method Deficiencies: None

2.9 PHARMACOKINETIC (PK) DATA ANALYSIS:

PK Parameters: AUC_{0-t} (AUC), $AUC_{0-infinity}$ (AUCI), C_{max}, T_{max}, elimination $t_{1/2}$ and K_{el} were computed.

2.10 RESULTS:

Clinical Study Conduct:

Number of subject dosed:	18
Number of subjects completing the study:	16 (subjects #13 and 14 withdrew for personal reasons).
Adverse events:	Twenty one (21) adverse events were reported during the study. Six events were judged to be unrelated to the study drug. The distribution of the remaining was similar between two products (vol. 1.3).
Protocol deviations:	Incidences of deviations from scheduled blood sampling times were reported (vol. 1.3). In the reviewer's opinion, these deviations should not affect bioavailability comparisons.

PK Data:

Individual-subject plasma concentration data: Albuterol plasma concentration data are given in appendix 2 (vol. 1.3). Line graphs depicting individual-subject concentration vs. time profiles are included in the same section. The slope and intercept values for Kel determinations and time points for calculation of Kel values are listed also in the same section.

Mean plasma concentration profiles: See table 4 (attachment).

AUC, AUCI and C_{max} data: See table 5 (attachment) for individual subject values, AUC/AUCI ratios and Test/Reference ratios of AUC, AUCI and C_{max}.

Bioavailability Comparisons::

Mean parametric values and test/ref ratios: see table 6 (attachment).

Deficiencies in the non-fasting study: None

3. Single-dose Fasting Bioequivalence Study on the 4-mg tablet (#2396)

3.1 OBJECTIVE: The purpose of this study was to establish bioequivalence of Sidmak Laboratories' albuterol sulfate **4-mg** extended release tablets to Muro 's Volmax® **4-mg** extended release tablets.

3.2 STUDY SITE, INVESTIGATORS AND DATES:

Clinical & Analytical study site: Same as study #1466.

Medical Director: ———————, MD.
Analytical Director: ———————

Study Protocol: Protocol (#002396, October 18, 2000, Appendix 1, vol. 1.1) was approved by the ——————— Institutional Review Board.

Dosing Dates: November 17 and December 3, 2000
Analytical Dates: December 14, 2000 – January 2, 20001

3.3 SUBJECT SELECTION:

Forty (40) healthy male volunteers were enrolled for this study. The mean age and weight of these volunteers were 25 years and 77.2 kg respectively (vol. 1.1). Subjects who entered this study were selected based on acceptable medical history, physical examination and normal clinical laboratory tests for hematopoietic, hepatic and renal functions, and appropriate subject selection criteria outlined in the study protocol.

3.4 STUDY DESIGN: The clinical study was conducted as a single dose, randomized, two-treatment, two-period crossover evaluation with a washout period of 14 days between the two dosing days.

3.5 TREATMENTS:

A: Albuterol sulfate extended release tablets 1x4 mg, Sidmak Laboratories, Lot #: 00-039T, Lot Size: ——— tablets, Content uniformity: 97.7%, Potency 98.9%.

B: Volmax® extended release tablets 1x4-mg, Muro , Lot #: D008194, Lot Size: Commercial lot, Expiry Date – October 2001, Content uniformity: 97.0 %, Potency 95.5% .

The randomization sequence used in the study is given in the table 8 (attachment).

3.6 DOSING: After an overnight (10 hours) fast, each drug was given orally with 240 mL of water. Within one hour before and one hour after dosing, the only water supplied was with drug administration. Subjects were confined to the clinical facility until 24 hours after dosing. They returned for subsequent blood samples.

3.7 SAMPLE COLLECTION AND STORAGE:

Sample:	Blood samples were collected under condition to minimize exposure to light.
Sampling times:	0 (pre-dose) and 0.75, 1.5, 2.25, 3, 3.75, 4.5, 5.25, 6, 7, 8, 10, 12, 16, 24, 36, 48 and 60 hours post-dose (18 samples).
Sample Storage:	Plasma was separated and stored at -20 ± 10 °C until analysis.

3.8 HEMODYNAMIC EVALUATIONS: Not reported.

ANALYTICAL PROCEDURE (Not to be released under FOI):

3.9 Method: Same as study #2397

Calibration Standards' (CS) and Quality Control (QC) samples' concentrations for study sample analyses:

CS ———————————————————————————

QC ———————————————

Specificity: No interfering peaks were detected in representative chromatograms for the blank plasma samples and the zero-hour study samples

Limit of Quantitation: Same as study #2397

Linearity: Calibration curves were linear in the range of calibration standards used (——— vol. 1.1).

Recovery and Stability: Same as study #2397

Reproducibility and Accuracy (Inter-day (Within the sample analysis period, , vol. 1.1):

	Precision	Accuracy
Based on CS:	———	———
Based on QC samples:	———	———

Repeat Assays: A total of 41 samples were re-analyzed for a variety of reasons including 6 samples analyzed for anomalous values (vol. 1.1). Of these 6 samples, 3 were reported as below the limit of quantitation and the remaining were reported as repeat-assay values. None of these three values represent Cmax data. In the reviewer's opinion the impact of the use of repeat-assay values on AUC values should be negligible.

Analytical Method Deficiencies: None

3.10 PHARMACOKINETIC (PK) DATA ANALYSIS AND STATISTICAL ANALYSIS: Same as study #1466.

3.11RESULTS:

Clinical Study Conduct:

Number of subjects dosed:	40
Number of subjects completing the study:	39 (Subject #5 failed ethanol test before period 2). However, as per protocol, plasma samples from 36 subjects were analyzed.
Adverse events:	Eight (8) adverse events were reported, of which four were probably related to drug treatment (Test: Anxiety, agitation and headache, Ref.: Anxiety).
Protocol deviations:	Minor deviations related to blood draw times were reported for 23 samples. In all cases nominal times were used for computation of AUCs.

PK Data:

Individual-subject plasma concentration data: Albuterol plasma concentration data are given in appendix 2 (vol. 1.1). Line graphs depicting individual-subject concentration vs. time profiles are included in the same section. The slope and intercept values for Kel determinations, and time points for calculation of Kel values are also listed in the same section.

Mean plasma concentration profiles: See table 7 (attachment).

AUC, AUCI and C_{max} data: See table 8 (attachment) for individual subject values, AUC/AUCI ratios and Test/Reference ratios of AUC, AUCI and C_{max}.

Bioequivalence Evaluation: Bioequivalence evaluation is based on 36 subjects' data.

Mean parametric values and test/ref ratios: See table 9 (attachment).

90% confidence intervals: The 90% confidence intervals for AUC, AUCI and C_{max} were within the acceptable limit of 80-125% (table 9, attachment).

Sequence Effect: Not detected based on reviewer's analyses.

Deficiencies in the bioequivalence study: None

4. Multiple-dose (Steady-State) Bioequivalence Study (#2398) on the 8-mg tablet

4.1 OBJECTIVE: The purpose of this study was to establish steady-state bioequivalence of Sidmak Laboratories' albuterol sulfate **8-mg** extended release tablets to Muro's Volmax® **8-mg** extended release tablets.

4.2 STUDY SITE, INVESTIGATORS AND DATES:

Clinical & Analytica study site: Same as study #1466.

Medical Director: _____ MD.
Analytical Director: _____

Study Protocol: Protocol (#002398, October 18, 2000, Appendix 1, vol. 1.9) was approved by the _____ Institutional Review Board.

Dosing Dates: November 8 and December 22, 2000
Analytical Dates: January 1 – February 1, 2001

4.3 SUBJECT SELECTION:

Forty three (43) healthy male volunteers were enrolled for this study. The mean age and weight of these volunteers were 29 years and 78.0 kg, respectively (vol. 1.9). Subjects who entered this study were selected based on acceptable medical history, physical examination and normal clinical laboratory tests for hematopoietic, hepatic and renal functions, and appropriate subject selection criteria outlined in the study protocol.

4.4 STUDY DESIGN: The clinical study was conducted as a multiple-dose, randomized, two-treatment, two-period crossover evaluation with a washout period of 14 days between the two dosing days.

4.5 TREATMENTS:

A: Albuterol sulfate extended release tablets 1X8 mg, Sidmak Laboratories, Lot #: 00-016T.

B: Volmax® extended release tablets 1x8 mg, Muro , Lot #: 10460727.

The randomization sequence used in the study is given in the table 11 (attachment).

4.6 DOSING: At 0 hour of days 1-6 and at hour 12 on day 1-5 the designated treatments were administered orally with 240 mL of water.

4.7 SAMPLE COLLECTION AND STORAGE:

Sample:	Blood samples were collected under conditions to minimize exposure to light.
Sampling times:	0 (pre-dose) on day 1, 4, 5 and 6 and at 1, 2, 3, 3.75, 4.5, 5.25, 6.75, 7.5, 8.25, 10 and 12hours post-dose .
Sample Storage:	Plasma was separated and stored at -20 ± 10 °C until analysis.

4.8 HEMODYNAMIC EVALUATIONS: Not reported.

4.9 ANALYTICAL PROCEDURE (Not to be released under FOI):

Method: Same as study #1466

Calibration Standards' (CS) and Quality Control (QC) samples' concentrations for study sample analyses:

CS [redacted]
QC [redacted]

Specificity: No interfering peaks were detected in representative chromatograms for the blank plasma samples and the zero-hour study samples

Limit of Quantitation: Same as study #1466

Linearity: Calibration curves were linear in the range of calibration standards used ([redacted] vol. 1.10).

Recovery and Stability: Same as study #1466

Reproducibility and Accuracy (Inter-day (Within the sample analysis period, , vol. 1.10):

	Precision	Accuracy
Based on CS:	_____	_____
Based on QC samples:	_____	_____

Repeat Assays: A total of 12 samples were re-analyzed for a variety of reasons including 1 sample analyzed for anomalous values (vol. 1.10). The original-assay value was reported for that sample.

Analytical Method Deficiencies: None

4.10 PHARMACOKINETIC (PK) DATA ANALYSIS AND STATISTICAL ANALYSIS: Same as study #2396, with the exception of AUCI (not calculated for this study), Cmin and % fluctuation [Flux 1 = ((Cmax-Cmin)/Cssav)x100) and Flux 2 = ((Cmax-Cmin)/Cmin)x100)]. The reviewer's analysis of variance was performed in two steps, because the subjects were dose in two groups on separate days. In the first step, the Group*TRT interaction was used in the ANOVA model, and that term was found to be insignificant ($p \geq 0.3$). Therefore, AUC and Cmax data were analyzed without the Group*TRT term.

4.11 RESULTS:

Clinical Study Conduct:

Number of subjects dosed:	43
Number of subjects completing the study:	37 (Subjects 4, 19, 31 and 34 were withdrawn from the study by the medical officer due to adverse events. Subject 27 was withdrawn due to a positive urine drug test, Subject 45 withdrew for personal reasons).
Adverse events:	A variety of clinical events were reported in a number of subjects (vol. 1.9). Many events were unrelated to drug treatments. Distribution of drug-related events was approximately the same between the two treatments

Protocol deviations: Minor deviations related to blood draw times were reported for 80 samples. In all cases nominal times were used for computation of AUCs.

PK Data:

Individual-subject plasma concentration data: Albuterol plasma concentration data are given in appendix 2 (vol. 1.9). Line graphs depicting individual-subject concentration vs. time profiles are included in the same section.

Mean plasma concentration profiles: See table 10 (attachment).

AUC and C_{max} data: See table 11 (attachment) for individual subject values and Test/Reference ratios of AUC and C_{max}.

Bioequivalence Evaluation: Bioequivalence evaluation is based on 36 subjects' data.

Mean parametric values and test/ref ratios: See table 12 (attachment).

90% confidence intervals: The 90% confidence intervals for AUC and C_{max} were within the acceptable limit of 80-125% (table 12, attachment).

Sequence Effect: Not detected based on reviewer's analyses.

Deficiencies in the bioequivalence study: None

5. *In Vitro* Dissolution Testing

Method: Dissolution testing was performed using the USP apparatus II (paddle) operated at 50 rpm

Test and reference products: Lots of the test and reference products used for dissolution testing and the bioequivalence study were identical (see the table blow for lot numbers)

Results: Dissolution data are listed below. The firm tested dissolution in [redacted]. For the extended release products, the Agency recommends dissolution testing in different media. The dissolution testing is unacceptable.

In vitro Dissolution Testing (Sponsor's Method)

Drug Product: Albuterol Sulfate Extended Release Tablets
Dose Strength: 8 and 4-mg

ANDA # 76-130, the raw data are given in vol. 1.1
Firm: **Sidmak Laboratories**
Submission Date: March 2, 2001, 2000
File # **7601305SDW.301**

F_2 Values (T vs. R)	
Product	**F_2 Value**
8-mg	68.42
4-mg	54.03

Conditions of Dissolution Testing:

USP Apparatus II Paddle, RPM: 50
Units Tested: 12
Media: ~~~~
Specifications: USP or FDA have not established specifications

Reference Drug: Volmax^R 8 and 4-mg tablets

Results of Dissolution Testing:

Sampling Time (Hr)	Test Product (T) Lot # 0016T Strength: 8-mg			Reference Product (R) Lot # 10460727 Strength: 8-mg			T/R
	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV	
1	3		42.3	10		8.9	**0.30**
2	23		13.8	23		7.3	**1.00**
4	51		4.6	50		5.9	**1.02**
6	70		3.0	73		5.2	**0.96**
8	83		2.1	89		3.6	**0.93**
10	92		2.3	95		3.9	**0.97**

Sampling Time (Hr)	Test Product (T) Lot # 00-039T Strength: 4-mg			Reference Product (R) Lot # D008194 Strength: 4-mg			T/R
	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV	
1	1		0.0	9		10,0	**0.11**
2	7		56.2	22		11.3	**0.32**
4	44		5.8	47		8.9	**0.94**
6	65		3.7	70		7.4	**0.93**
8	78		2.7	85		5.5	**0.92**
10	87		1.8	93		4.1	**0.94**

6. Waiver Request: N/A.

7. Test Products' Compositions (Not to be released under FOI):

Ingredient	Product	
	4-mg tablets	8-mg tablet
Albuterol sulfate, USP	4.8 mg[1]	9.6 mg[1]
Lactose monohydrate, NF Calcium Sulfate, NF Ethyl Cellulose, NF		
Stearic Acid, NF Magnesium Stearate, NF Hydroxypropyl Methylcellulose, USP Triacetin, USP Propylene Glycol, USP Carnauba Wax, NF Green Black Ink Ink Thinner XI		
Total	117.788 mg	113.893 mg

4.8 mg of albuterol sulfate USP provides 4 mg of albuterol. The potency of all inactive ingredients is within the range used in the approved tablet products intended for oral administration, based on the IIG.
** Lost during processing.*
The test product 4-mg tablet is green and round, printed SL on one side and 45 on the other side in black ink. Its 8-mg green and round printed SL on one side and 46 on the other side in black ink.
The reference product 4-mg tablet is light blue and hexagonal, printed Volmax on one side and 4 on the other side in black ink. Its 8-mg green and white printed Volmax on one side and 8 on the other side in black ink.

Comments

1. This firm conducted a fasting bioequivalence study on its albuterol sulfate 8-mg extended release tablet and the reference product, Volmax® 8-mg extended release tablet in 24 healthy subjects. Bioequivalence evaluation was based on AUC, AUCI and C_{max} data for 21 subjects. Based on reviewer's calculations, the AUC, AUCI and C_{max} 90% confidence intervals were within the acceptable limit of 80-125%.

2. The sponsor also compared the bioavailability of the 8-mg tablets of the test and reference products after ingestion of a high fat meal in 18 subjects. The results of this study (based on 16 subjects' data) demonstrate comparable bioavailability of the test and reference products under non-fasting conditions.

3. This firm conducted a multiple dose (steady-state) study on its albuterol sulfate 8-mg extended release tablet and the reference product, Volmax® 8-mg extended release tablet in 43 healthy subjects. Bioequivalence evaluation was based on AUC and C_{max} data for 36 subjects. Based on reviewer's calculations, the AUC, and C_{max} 90% confidence intervals were within the acceptable limit of 80-125%. It is noted, however, that a multiple-dose study is not required for approval of extended-release tablets. The review of the study is presented for completeness of information.

4. This firm conducted a fasting bioequivalence study on its albuterol sulfate 4-mg extended release tablet and the reference product, Volmax® 4-mg extended release tablet in 39 healthy subjects. Bioequivalence evaluation was based on AUC, AUCI and C_{max} data for 36 subjects. Based on reviewer's calculations, the AUC, AUCI and C_{max} 90% confidence intervals were within the acceptable limit of 80-125%.

5. The *in vitro* dissolution conducted by the firm on albuterol sulfate 8-mg and 4-mg extended release tablets is unacceptable. The firm should conduct dissolution testing on 12 units of test and reference products using the USP apparatus II (Paddle, 50 rpm) in different dissolution media (e.g., water, 0.1N HCl and buffers at pH 4.5 and 6.8).

8. Recommendations

1. The *in-vivo* bioequivalence study conducted under fasting condition by Sidmak Laboratories on its albuterol sulfate 8-mg extended release tablet, lot #00-016T, comparing it to the reference product Volmax® 8-mg extended release tablet, lot #1046027, manufactured by Muro, has been found to be acceptable to the Division of Bioequivalence. The study demonstrates that under fasting conditions, Sidmak Laboratories' albuterol sulfate 8-mg extended release tablets are bioequivalent to Volmax® 8-mg extended release tablets, manufactured by Muro.

2. The *in-vivo* study conducted under non- fasting condition by Sidmak Laboratories comparing bioavailability of its albuterol sulfate 8-mg extended release tablet, lot # lot #00-016T, to that of the reference product Volmax® 8-mg extended release tablet, lot #1046027, manufactured by Muro , has been found to be acceptable to the Division of Bioequivalence. The study demonstrates that under non-fasting conditions, bioavailability of Sidmak Laboratories' albuterol sulfate 8-mg extended release tablets is similar to that of Volmax® 8-mg extended release tablets, manufactured by Muro.

3. The *in-vivo* bioequivalence study conducted under fasting condition by Sidmak Laboratories on its albuterol sulfate 4-mg extended release tablet, lot #0039T, comparing it to the reference product Volmax® 4-mg extended release tablet, lot #D00894, manufactured by Muro, has been found to be acceptable to the Division of Bioequivalence. The study demonstrates that under fasting conditions, Sidmak Laboratories' albuterol sulfate 4-mg extended release tablets are bioequivalent to Volmax® 4-mg extended release tablets, manufactured by Muro.

4. The *in vitro* dissolution testing conducted by Sidmak Laboratories on its albuterol sulfate 8-mg and 4-mg tablets is unacceptable. The firm should conduct dissolution testing on 12 units of test and reference products using the USP apparatus II (Paddle, 50 rpm) in different dissolution media (e.g., water, 0.1N HCl and buffers at pH 4.5 and 6.8. The firm may refer to the following Agency Guidances:

   Bioavailability and bioequivalence studies for orally administered drug products – General Considerations (10/2000)

   Extended release oral dosage forms: Development, evaluation and application of in vitro-in vivo correlations (9/1997)

From the bioequivalence point of view, the firm has met the requirements of *in vivo* bioequivalence on its albuterol sulfate 8-mg and 4-mg extended release tablet. However, the in vitro dissolution testing is unacceptable. Therefore, from the bioequivalence point of view, the application is incomplete.

Gur J.P. Singh, Ph.D.
Review Branch II, Division of Bioequivalence.

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR 6/8/2001

CONCUR: DATE: 6/14/2001
for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence.

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BIOEQUIVALENCY DEFICIENCY

ANDA/AADA: 76-130 APPLICANT: Sidmak Laboratories

DRUG PRODUCTS: Albuterol sulfate extended release tablets, 4-mg and 8-mg

The Division of Bioequivalence has completed its review of submission (s) acknowledged on the cover sheet. The following deficiency has been identified.

The dissolution testing on your albuterol sulfate 4-mg and 8-mg tablets is unacceptable. You should conduct dissolution testing on 12 units of test and reference products using the USP apparatus II (Paddle, 50 rpm) in different dissolution media (e.g., water, 0.1N HCl and buffers at pH 4.5 and 6.8). You may refer to the following Agency Guidances:

Bioavailability and bioequivalence studies for orally administered drug products - General Considerations (10/2000)

Extended release oral dosage forms: Development, evaluation and application of in vitro-in vivo correlations (9/1997)

Sincerely yours,

for Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA: 76-130
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD-655/Reviewer GPS 5/24/01
HFD-655/Bio Team Leader
HFD-617/Project Manager
HFD-650/Dale Conner for RVP 6/14/2001

6/8/01

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BIOEQUIVALENCY - ACCEPTABLE **Submission date: 3/2/2001**

1. **FASTING STUDY** (STF)
Clinical:
Analytical
Strength: 8-mg
Outcome: AC

2. **NON-FASTING STUDY** (STP)
Clinical:
Analytical:
Strength: 8-mg
Outcome: AC

3. **FASTING STUDY** (STF)
Clinical:
Analytical
Strength: 4-mg
Outcome: AC

4. **MULTIDOSE STUDY** (STM)
Clinical:
Analytical
Strength: 8-mg
Outcome: AC

DISSOLUTION DATA (DIS)
Strength: 4-mg and 8-mg
Outcome: UN

WinBio Comments: The fasting and non-fasting bioequivalence studies are acceptable. Dissolution testing on the 4-mg and 10 mg tablets is unacceptable.

Table 1: Albuterol mean plasma concentrations (Study #1466, ANDA 76130, N = 21)

Treat	TEST Mean	%CV	REF Mean	%CV	T/R
0	0	-	0.00	-	
0.75	101.81	71.67	438.64	61.74	-
1.5	1310.30	54.15	1298.06	41.70	2.99
2.25	3833.91	40.49	2998.60	41.09	2.95
3	5900.55	38.77	4859.42	33.21	1.97
3.75	7717.70	21.46	6068.43	24.64	1.59
4.5	9000.40	28.65	7929.21	28.48	1.48
5.25	7828.78	35.73	8395.05	42.78	0.99
6	6856.26	36.85	8093.20	40.75	0.82
7	6066.79	35.31	7530.17	40.69	0.75
8	5423.08	34.35	6518.51	38.57	0.72
10	4220.00	29.79	4884.54	35.48	0.65
12	3207.86	24.48	3748.90	31.67	0.66
16	2322.12	18.30	2604.51	25.52	0.62
24	1511.41	16.93	1521.08	21.30	0.58
36	761.47	37.81	720.47	37.56	0.50
48	370.41	49.14	338.03	60.44	0.51
60	170.97	66.67	163.17	88.605	0.51

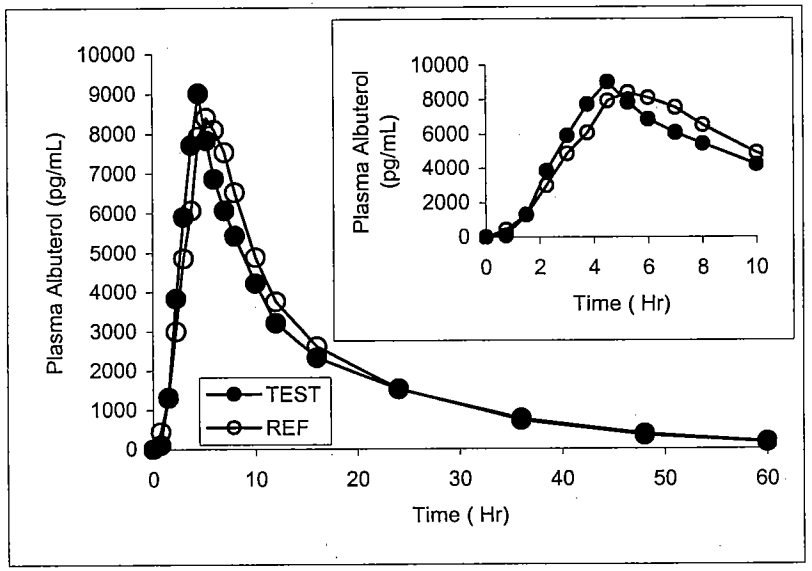

Table 2: Individual Parameter Values (Study #1466, ANDA 76-130, N = 21)

										TEST/REF		
subj	seq	Treat	AUC (A)	AUCI (B)	A/B	CMAX	TMAX	KEL	THALF	AUC	AUCI	CMAX
1	BA	A	94529	95108	0.99	9186.80	4.50	0.09	7.76	1.04	1.03	1.02
2	AB	A	94830	96264	0.99	8895.40	3.00	0.07	9.60	0.89	0.87	0.98
3	BA	A	85314	87494	0.98	6301.20	2.25	0.07	10.53	0.97	0.98	0.82
4	BA	A	90912	96108	0.95	8006.70	3.00	0.05	13.16	0.73	0.76	0.75
5	BA	A	126601	128028	0.99	12077.20	4.50	0.07	9.89	1.10	1.04	1.36
6	AB	A	96077	101709	0.94	9099.10	4.50	0.05	13.50	0.73	0.77	0.51
8	AB	A	111349	114341	0.97	11054.20	4.50	0.06	12.48	1.00	0.95	1.45
9	AB	A	131822	134741	0.98	14615.10	5.25	0.06	11.45	0.88	0.87	1.62
10	AB	A	135574	137436	0.99	11708.90	6.00	0.07	10.15	1.19	1.20	1.27
12	AB	A	133321	138563	0.96	8309.10	3.75	0.06	11.38	0.95	0.98	0.65
13	BA	A	104415	106348	0.98	14439.50	4.50	0.07	10.45	1.20	1.21	1.74
14	BA	A	111484	113563	0.98	11349.10	3.00	0.07	9.80	0.77	0.77	0.90
15	AB	A	102858	103800	0.99	10162.60	3.75	0.08	8.78	1.21	1.16	2.47
16	BA	A	80742	87535	0.92	7012.30	4.50	0.07	9.54	0.80	0.85	0.86
17	AB	A	81438	82448	0.99	9862.40	3.75	0.10	7.21	1.15	1.16	1.25
18	AB	A	117928	129809	0.91	11093.80	4.50	0.03	20.47	0.95	1.01	0.80
20	AB	A	99220	104114	0.95	7358.10	3.75	0.05	13.15	0.82	0.85	0.61
22	BA	A	118996	120296	0.99	9021.90	3.75	0.09	7.92	1.04	0.93	1.19
23	AB	A	122817	125270	0.98	9408.50	6.00	0.06	11.21	0.83	0.84	0.73
24	BA	A	96681	104774	0.92	6756.70	3.75	0.05	14.07	1.05	1.05	1.32
26	BA	A	137837	140327	0.98	14604.40	4.50	0.07	10.46	1.09	1.10	1.07
		Mean	**108321.19**	**111813.14**	**0.97**	**10015.38**	**4.14**	**0.07**	**11.09**	**# 0.97**	**0.97**	**1.11**
		%CV	**16.85**	**16.34**	**2.63**	**24.92**	**22.62**	**22.18**	**25.86**	**# 16.04**	**14.72**	**41.05**
1	BA	B	91228.00	92169.00	0.99	8996.90	5.25	0.08	8.30			
2	AB	B	106880.00	110052.00	0.97	9083.00	5.25	0.06	12.54			
3	BA	B	87736.00	89540.00	0.98	7729.50	4.50	0.07	10.02			
4	BA	B	125390.00	126031.00	0.99	10664.20	4.50	0.09	7.67			
5	BA	B	114994.00	123365.00	0.93	8861.10	5.25	0.05	14.82			
6	AB	B	131474.00	132545.00	0.99	17793.90	5.25	0.08	9.08			
8	AB	B	111832.00	120819.00	0.93	7646.90	6.00	0.04	16.84			
9	AB	B	149791.00	154749.00	0.97	9044.80	10.00	0.06	12.40			
10	AB	B	114117.00	114582.00	1.00	9221.10	4.50	0.09	7.30			
12	AB	B	139793.00	140702.00	0.99	12799.00	7.00	0.09	7.54			

13	BA	B	86740.00	87639.00	0.99	8287.70	3.75	0.08	8.36
14	BA	B	143878.00	147024.00	0.98	12582.10	7.00	0.06	11.39
15	AB	B	85095.00	89165.00	0.95	4120.30	3.75	0.06	11.40
16	BA	B	101254.00	103037.00	0.98	8111.90	4.50	0.09	7.61
17	AB	B	70533.00	71083.00	0.99	7867.90	3.75	0.10	6.69
18	AB	B	124519.00	128080.00	0.97	13945.20	6.00	0.05	13.61
20	AB	B	121253.00	123101.00	0.98	11987.10	6.00	0.07	9.45
22	BA	B	114321.00	129712.00	0.88	7598.50	3.75	0.04	19.48
23	AB	B	148099.00	148803.00	1.00	12872.90	7.00	0.09	7.64
24	BA	B	91931.00	100253.00	0.92	5104.60	3.75	0.05	13.86
26	BA	B	126642.00	128136.00	0.99	13619.30	5.25	0.08	9.24
		Mean	**113690.48**	**117170.81**	**0.97**	**9901.80**	**5.33**	**0.07**	**10.73**
		%CV	**19.81**	**19.43**	**3.21**	**32.49**	**28.68**	**28.08**	**32.38**

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Table 3: Parametric Data (ANDA 76-130, Fasting Study 1466, N=21)

Parameter	TEST (A)		REF (B)		A/B	90%- CI	ISV
	Mean	%CV	Mean	%CV			
AUC	108321.2	16.8	113690.5	19.8	**0.95**	**89.51-102.11**	11.75%
(ng/mL*hr)	*108158.9*		*113450.5*		***0.95***		
AUCI	111813.1	16.3	117170.8	19.4	**0.95**	**90.30-101.66**	10.65%
ng/mL*hr)	*111637.9*		*116967.2*		***0.95***		
CMAX	10015.4	24.9	9901.8	32.5	**1.01**	**88.85-118.39**	25.50%
(ng/mL)	*10009.0*		*9867.9*		***1.01***		
TMAX (hr)	4.1	22.6	5.3	28.7	**0.78**		
KEL (hr-1)	0.066	22.2	0.070	28.1	**0.93**		
THALF (hr)	11.1	25.9	10.7	32.4	**1.03**		

Data given in italics are based on LS means
ISV = Intrasubject Variability
All data are based on the reviewer's calculations
The 90% confidence interval are based on the log-transformed data

Table 4: Albuterol mean plasma concentrations (ANDA 76-130, Study #2397)

Time	A-TEST (Fast)		B-TEST (Fed)		C-REF (Fast)		B/A	B/C
(Hr)	Mean	%CV	Mean	%CV	Mean	%CV		
0	0	-	0	-	0	-		
1	229.98	101.34	17.48	193.00	304.43	73.78	0.08	0.06
2	3203.09	53.63	783.05	94.59	1432.86	43.26	0.24	0.55
3	5341.89	38.76	2703.34	53.44	2794.25	33.15	0.51	0.97
3.75	7187.93	40.83	3822.26	43.36	3521.79	26.65	0.53	1.09
4.5	8224.49	32.18	4853.86	39.62	4725.03	25.47	0.59	1.03
5.25	7704.74	36.16	6266.72	39.88	5761.68	23.71	0.81	1.09
6	6976.56	38.72	6701.56	31.06	6240.87	17.95	0.96	1.07
6.75	6139.60	33.41	6497.53	31.45	6417.20	21.93	1.06	1.01
7.5	6068.21	35.77	6633.83	33.58	6363.08	23.90	1.09	1.04
8.25	5157.56	31.86	6226.04	35.19	6082.59	24.50	1.21	1.02
9	5142.97	37.68	5824.58	35.29	5860.87	26.95	1.13	0.99
10	4245.78	29.70	5103.89	34.49	5362.86	28.41	1.20	0.95
14	2845.24	25.28	3457.34	31.52	3576.30	30.01	1.22	0.97
24	1439.71	29.37	1546.89	26.35	1555.26	19.54	1.07	0.99
36	686.18	35.82	687.49	22.16	684.01	25.75	1.00	1.01
48	351.91	52.53	356.60	43.97	340.70	45.40	1.01	1.05
60	173.31	72.71	163.53	72.62	156.66	84.89	0.94	1.04

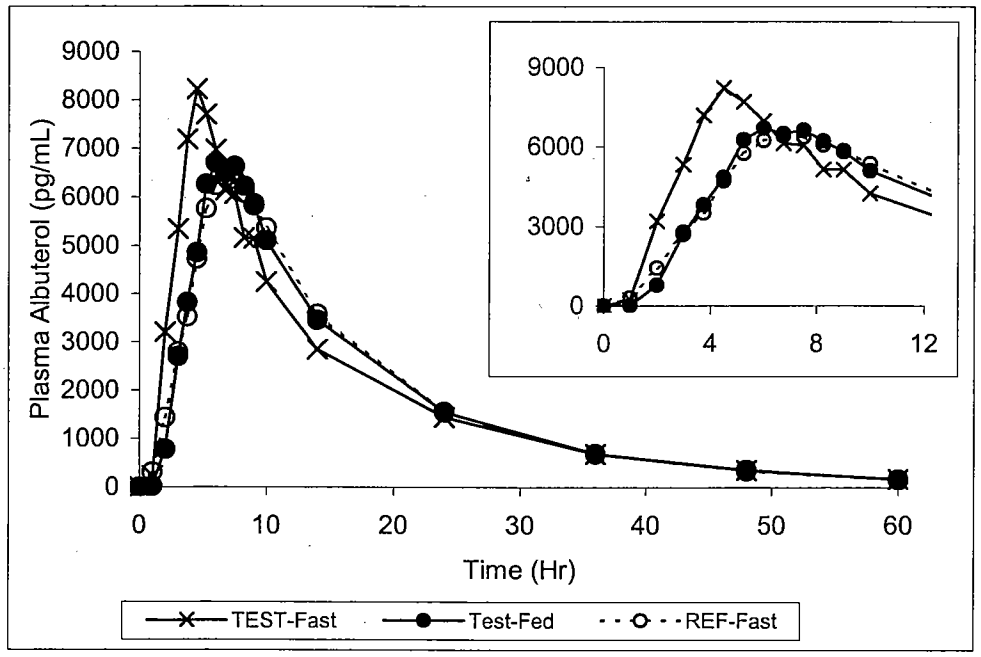

Table 5: Individual parameter values for albuterol (ANDA 76-130, Study #2397)

SUB	SEQ	TRT	AUC	AUCI	Ratio	CMAX	TMAX	KEL	T1/2
1	2	A	123190.00	124061.00	0.99	10939.70	3.75	0.08	8.52
2	3	A	119152.00	126512.00	0.94	9519.30	3.75	0.04	18.38
3	4	A	135560.00	137986.00	0.98	11499.80	6.00	0.07	10.56
4	2	A	95754.00	96855.00	0.99	10249.50	5.25	0.07	9.64
5	5	A	106295.00	109077.00	0.97	10677.50	4.50	0.06	11.51
6	2	A	93904.00	94536.00	0.99	8715.10	4.50	0.11	6.51
7	5	A	96975.00	97804.00	0.99	5025.60	3.00	0.09	7.61
8	1	A	124101.00	128091.00	0.97	10916.10	6.00	0.05	13.37
9	1	A	98141.00	104735.00	0.94	7120.60	3.75	0.05	14.66
10	4	A	92106.00	100308.00	0.92	7989.40	4.50	0.04	17.16
11	4	A	53093.00	54819.00	0.97	4947.10	3.00	0.05	12.97
12	5	A	85429.00	86829.00	0.98	6502.30	3.00	0.08	8.28
13	6	A	111723.00	113989.00	0.98	9639.70	5.25	0.05	13.02
15	3	A	113296.00	121506.00	0.93	11464.90	4.50	0.04	18.12
16	3	A	148349.00	158943.00	0.93	11598.50	3.75	0.04	15.65
17	6	A	127230.00	128108.00	0.99	13129.80	3.75	0.08	8.72
18	6	A	112938.00	113972.00	0.99	9959.60	9.20	0.08	8.61
Mean			*108072.71*	*111654.76*	*0.97*	*9405.56*	*4.56*	*0.06*	*11.96*
%CV			*20.41*	*20.87*	*2.66*	*25.19*	*33.48*	*32.19*	*32.01*
Geomean			*105616.64*	*109041.04*	*0.97*	*9075.48*	*4.36*	*0.06*	*11.39*
1	2	B	131412.00	132663.00	0.99	7258.60	8.25	0.08	8.59
2	3	B	94187.00	105135.00	0.90	7996.20	5.25	0.03	22.30
3	4	B	130955.00	132373.00	0.99	10167.90	5.25	0.08	9.01
4	2	B	68105.00	68610.00	0.99	3129.70	14.00	0.11	6.50
5	5	B	137388.00	138591.00	0.99	9187.70	7.50	0.08	8.39
6	2	B	81779.00	82953.00	0.99	6948.20	6.00	0.09	7.36
7	5	B	123992.00	125373.00	0.99	9112.90	8.25	0.08	8.53
8	1	B	86412.00	90027.00	0.96	5577.50	8.25	0.05	14.80
9	1	B	104369.00	109030.00	0.96	8054.60	6.00	0.05	13.86
10	4	B	119202.00	119917.00	0.99	8238.50	6.00	0.09	8.01
11	4	B	46952.00	48034.00	0.98	3328.10	3.00	0.07	10.16
12	5	B	109659.00	111641.00	0.98	6055.30	6.00	0.07	9.57
13	6	B	94167.00	106554.00	0.88	6470.40	6.75	0.03	22.85
15	3	B	115660.00	119280.00	0.97	8938.20	6.00	0.06	12.51
16	3	B	142684.00	150996.00	0.94	9890.50	5.25	0.04	16.00
17	6	B	117605.00	118056.00	1.00	8582.90	5.25	0.10	7.03
18	6	B	105378.00	112251.00	0.94	7200.00	6.75	0.04	15.77
Mean			*106465.06*	*110087.29*	*0.97*	*7419.84*	*6.69*	*0.07*	*11.84*
%CV			*24.07*	*23.52*	*3.52*	*27.44*	*34.59*	*35.10*	*42.89*
Geomean			*102950.33*	*106529.79*	*0.97*	*7081.60*	*6.38*	*0.06*	*10.96*
1	2	C	121679.00	122459.00	0.99	6795.30	8.25	0.09	7.63
2	3	C	103642.00	127047.00	0.82	7966.40	5.25	0.02	29.58
3	4	C	118816.00	124628.00	0.95	7716.00	9.00	0.05	15.34
4	2	C	93687.00	95236.00	0.98	6805.10	6.75	0.07	9.79
5	5	C	111415.00	112395.00	0.99	8500.00	7.50	0.08	8.49
6	2	C	79393.00	79891.00	0.99	6763.40	6.75	0.12	5.62

7	5	C	119238.00	120872.00	0.99	8773.30	9.17	0.08	9.16
8	1	C	113181.00	119029.00	0.95	6425.10	9.00	0.05	14.61
9	1	C	80027.00	86387.00	0.93	6097.10	5.25	0.04	17.76
10	4	C	131080.00	132705.00	0.99	8261.50	8.25	0.08	9.21
11	4	C	90096.00	90567.00	0.99	5854.30	8.25	0.09	7.68
12	5	C	108583.00	110471.00	0.98	5072.90	10.00	0.07	9.55
15	3	C	131170.00	133965.00	0.98	7960.80	8.25	0.06	12.31
16	3	C	119132.00	122667.00	0.97	7935.20	7.50	0.06	11.75
17	6	C	109767.00	110395.00	0.99	9410.70	6.75	0.09	7.85
18	6	C	87939.00	88514.00	0.99	5693.00	4.50	0.11	6.40
Mean			*107164.43*	*110809.28*	0.97	*7241.86*	*7.46*	*0.07*	*11.39*
%CV			*15.17*	*15.37*	*4.53*	*16.58*	*20.62*	*35.60*	*50.10*
Geomean			*105948.39*	*109503.87*	*0.97*	*7145.78*	*7.30*	*0.07*	*10.44*

SUB	SEQ	A/B			B/C		
		AUC	AUCI	Cmax	AUC	AUCI	Cmax
1	2	0.94	0.94	1.51	1.08	1.08	1.07
2	3	1.27	1.20	1.19	0.91	0.83	1.00
3	4	1.04	1.04	1.13	1.10	1.06	1.32
4	2	1.41	1.41	3.27	0.73	0.72	0.46
5	5	0.77	0.79	1.16	1.23	1.23	1.08
6	2	1.15	1.14	1.25	1.03	1.04	1.03
7	5	0.78	0.78	0.55	1.04	1.04	1.04
8	1	1.44	1.42	1.96	0.76	0.76	0.87
9	1	0.94	0.96	0.88	1.30	1.26	1.32
10	4	0.77	0.84	0.97	0.91	0.90	1.00
11	4	1.13	1.14	1.49	0.52	0.53	0.57
12	5	0.78	0.78	1.07	1.01	1.01	1.19
13	6	1.19	1.07	1.49	0.72	0.80	0.81
15	3	0.98	1.02	1.28	0.97	0.97	1.13
16	3	1.04	1.05	1.17	1.30	1.37	1.05
17	6	1.08	1.09	1.53	1.34	1.33	1.51
18	6	1.07	1.02	1.38	0.98	1.01	0.99
Mean		*1.05*	*1.04*	1.00	*1.00*	*1.00*	*1.03*
%CV		*19.82*	*18.54*	*57.77*	*22.82*	*22.75*	*24.98*
Geomean		*1.03*	*1.02*	*1.28*	*0.97*	*0.97*	*0.99*

Table 6: Parametric Data (ANDA 76-130, Non-fasting Study 2397, N=16)

Parameter	TRT-A		TRT-B		TRT-C		B/C	B/A
	Mean	%CV	Mean	%CV	Mean	%CV		
AUCT	108072.71	20.41	106465.06	24.07	107164.43	15.17	**0.99**	0.99
(pg/ml*hr)	***105616.64***		***102950.33***		***105948.39***		***0.97***	***0.97***
AUCINF	111654.76	20.87	110087.29	23.52	110809.28	15.37	**0.99**	0.99
(pg/ml*hr)	***109041.04***		***106529.79***		***109503.87***		***0.97***	***0.98***
CMAX (pg/mL)	9405.56	25.19	7419.84	27.44	7241.86	16.58	**1.02**	0.79
	9075.48		***7081.60***		***7145.78***		***0.99***	***0.78***
TMAX (Hr)	4.56	33.48	6.69	34.59	7.46	20.62	**0.90**	1.47
KEL	0.0639	32.19	0.0676	35.10	0.0712	35.60	**0.95**	1.06
THALF (Hr)	11.96	32.01	11.84	42.89	11.39	50.10	**1.04**	0.99

Data given in italics are based on geometric means

Table 7: Albuterol mean plasma concentrations (Study #2396, ANDA 76130, N = 36)

Treat	TEST Mean	%CV	REF Mean	%CV	T/R
0	0	-	0	-	
0.75	12.08	332.18	207.24	58.34	0.06
1.5	169.98	88.64	766.15	47.00	0.22
2.25	836.11	96.73	1521.06	54.86	0.55
3	2254.64	64.79	2187.33	44.24	1.03
3.75	3131.43	51.37	3132.81	32.71	1.00
4.5	3693.66	37.88	4017.94	29.41	0.92
5.25	3248.52	33.92	3678.86	33.12	0.88
6	3022.23	37.44	3284.34	38.17	0.92
7	2670.11	35.60	3003.35	39.13	0.89
8	2432.73	35.92	2665.31	37.79	0.91
10	1892.03	31.82	2139.03	31.40	0.88
12	1577.09	33.70	1721.74	30.26	0.92
16	1200.44	33.58	1234.71	26.40	0.97
24	806.85	24.79	781.28	25.62	1.03
36	462.77	36.05	410.46	38.48	1.13
48	265.99	52.74	218.00	53.18	1.22
60	136.57	86.79	98.51	86.75	1.39

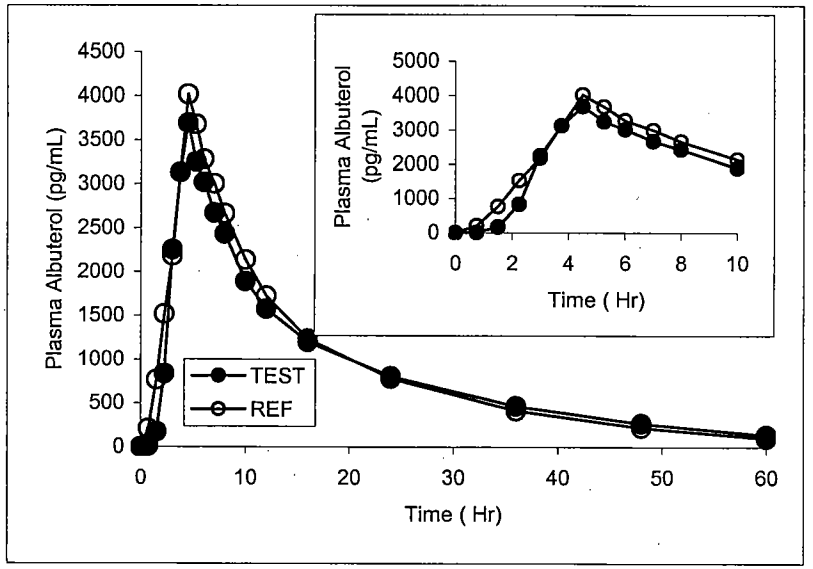

Table 8: Individual Parameter Values (Study #2396, ANDA 76130, N = 36)

			TEST				REF						
Subj	Seq	Treat	AUC (A)	AUCINF (B)	A/B	CMAX	AUC (C)	AUCINF (D)	C/D	CMAX	AUC	AUCINF	CMAX
1	AB	A	44908.00	46688.00	0.96	4300.80	38006.00	38670.00	0.98	3806.50	1.18	1.21	1.13
2	AB	A	67776.00	68749.00	0.99	6135.30	63191.00	63777.00	0.99	4725.90	1.07	1.08	1.30
3	AB	A	57578.00	59218.00	0.97	3722.60	48756.00	50455.00	0.97	3510.30	1.18	1.17	1.06
4	AB	A	67548.00	74770.00	0.90	4968.20	64343.00	67718.00	0.95	4363.70	1.05	1.10	1.14
6	BA	A	43425.00	44953.00	0.97	5020.20	42531.00	43013.00	0.99	4089.20	1.02	1.05	1.23
7	AB	A	83489.00	84713.00	0.99	4641.30	77659.00	78400.00	0.99	4073.20	1.08	1.08	1.14
8	AB	A	51859.00	56870.00	0.91	3642.30	41567.00	42903.00	0.97	2942.00	1.25	1.33	1.24
9	AB	A	53755.00	54947.00	0.98	6291.50	57490.00	59938.00	0.96	5323.20	0.94	0.92	1.18
10	BA	A	38345.00	40459.00	0.95	3501.40	62227.00	62749.00	0.99	5568.50	0.62	0.64	0.63
11	AB	A	49697.00	51452.00	0.97	4270.10	52864.00	53792.00	0.98	4921.80	0.94	0.96	0.87
12	BA	A	34008.00	34561.00	0.98	3302.50	47371.00	47935.00	0.99	5502.20	0.72	0.72	0.60
13	BA	A	50957.00	52633.00	0.97	5625.50	44133.00	44599.00	0.99	4068.20	1.15	1.18	1.38
14	AB	A	71251.00	74555.00	0.96	5917.90	72787.00	74749.00	0.97	7177.90	0.98	1.00	0.82
15	BA	A	47660.00	48398.00	0.98	5366.30	45402.00	56351.00	0.81	3357.90	1.05	0.86	1.60
16	AB	A	64350.00	70291.00	0.92	6024.50	45628.00	46181.00	0.99	3504.20	1.41	1.52	1.72
17	BA	A	50396.00	54547.00	0.92	5528.00	60920.00	64245.00	0.95	5846.50	0.83	0.85	0.95
18	AB	A	32147.00	32912.00	0.98	1653.90	45656.00	46581.00	0.98	3637.00	0.70	0.71	0.45
19	BA	A	53902.00	55522.00	0.97	4452.50	61056.00	62837.00	0.97	5841.90	0.88	0.88	0.76
20	BA	A	47833.00	52241.00	0.92	3536.30	50062.00	55582.00	0.90	3310.60	0.96	0.94	1.07
21	AB	A	59262.00	65521.00	0.90	6637.40	64192.00	69888.00	0.92	5069.80	0.92	0.94	1.31
22	BA	A	51752.00	61733.00	0.84	4015.40	55375.00	61710.00	0.90	4009.40	0.93	1.00	1.00
23	AB	A	69346.00	89955.00	0.77	4085.40	89775.00	96041.00	0.93	6864.90	0.77	0.94	0.60
24	BA	A	45213.00	45802.00	0.99	4127.60	43147.00	44679.00	0.97	2176.50	1.05	1.03	1.90
26	AB	A	62743.00	64044.00	0.98	4946.40	61905.00	62824.00	0.99	7021.70	1.01	1.02	0.70
27	AB	A	47162.00	49406.00	0.95	3234.30	43322.00	47052.00	0.92	2936.40	1.09	1.05	1.10
28	BA	A	41056.00	48370.00	0.85	3159.30	50441.00	51561.00	0.98	4634.40	0.81	0.94	0.68
29	AB	A	50843.00	56063.00	0.91	5550.10	54533.00	60990.00	0.89	5171.40	0.93	0.92	1.07
30	BA	A	52225.00	55830.00	0.94	6223.70	45268.00	46571.00	0.97	4567.30	1.15	1.20	1.36
31	AB	A	42028.00	43858.00	0.96	3956.80	35154.00	36114.00	0.97	3835.50	1.20	1.21	1.03
32	BA	A	46562.00	48073.00	0.97	5140.80	50695.00	53191.00	0.95	4574.10	0.92	0.90	1.12
33	AB	A	59849.00	64891.00	0.92	3814.30	60570.00	65565.00	0.92	3855.00	0.99	0.99	0.99
34	BA	A	54097.00	57428.00	0.94	3739.40	60031.00	66359.00	0.90	3772.80	0.90	0.87	0.99
35	BA	A	42702.00	43411.00	0.98	3545.50	49550.00	50672.00	0.98	5263.10	0.86	0.86	0.67
36	BA	A	53413.00	71163.00	0.75	1804.10	61961.00	64893.00	0.95	3951.70	0.86	1.10	0.46
38	BA	A	44149.00	50699.00	0.87	3046.50	52566.00	56606.00	0.93	4009.20	0.84	0.90	0.76
40	BA	A	45157.00	46797.00	0.96	4263.50	49445.00	49954.00	0.99	5707.10	0.91	0.94	0.75
		Mean	**52178.97**	**56153.42**	**0.94**	**4421.99**	**54154.97**	**56809.58**	**0.96**	**4527.53**	**0.98**	**1.00**	**1.02**
		%CV	**20.91**	**22.90**	**6.18**	**27.40**	**21.04**	**21.50**	**4.15**	**25.74**	**16.83**	**17.32**	**32.86**

Table 9: Parametric Data (ANDA 76-130, Fasting Study 2396, N=36)

Parameter	TEST (A)		REF (B)		A/B	90%- CI	ISV
	Mean	%CV	Mean	%CV			
AUC	52179.0	20.9	54155.0	21.0	**0.96**	**91.71-100.79**	10.93%
(ng/mL*hr)	*52178.9*		*54154.9*		***0.96***		
AUCI	56153.4	22.9	56809.6	21.5	**0.99**	**93.95-103.05**	10.29%
ng/mL*hr)	*56153.4*		*56809.6*		***0.99***		
CMAX	4422.0	27.4	4527.5	25.7	**0.98**	**93.95-103.05**	22.38%
(ng/mL)	*4421.9*		*4527.5*		***0.98***		
TMAX (hr)	4.5	27.4	4.7	20.3	**0.96**		
KEL (hr-1)	0.056	37.6	0.064	38.0	**0.88**		
THALF (hr)	14.3	41.0	12.6	42.8	**1.13**		

Data given in italics are based on LS means
ISV = Intrasubject Variability
All data are based on the reviewer's calculations
The 90% confidence interval are based on the log-transformed data

Table 10: Albuterol mean plasma concentrations (Study #2398, ANDA 76130, N = 36)

Treat	TEST Mean	%CV	REF Mean	%CV	T/R
-120	0	-	0.00	-	
-48	8382.07	25.10	8688.12	22.36	0.96
-24	8601.98	25.23	8602.54	25.08	1.00
0	8381.26	24.39	9434.10	25.61	0.89
1	8343.02	24.71	9360.26	21.91	0.89
2	10224.14	21.16	10248.31	22.38	1.00
3	12445.34	27.14	12105.87	22.77	1.03
3.75	13527.16	23.51	12711.20	21.88	1.06
4.5	14215.47	20.80	13512.48	21.39	1.05
5.25	13441.43	23.44	13271.56	23.67	1.01
6	12216.70	25.03	12308.40	25.79	0.99
6.75	11490.49	25.53	11756.17	26.04	0.98
7.5	10995.69	26.72	11180.84	24.29	0.98
8.25	9924.94	26.53	10257.84	24.45	0.97
10	8584.57	25.67	8702.31	23.75	0.99
12	7462.51	25.66	7508.92	22.33	0.99

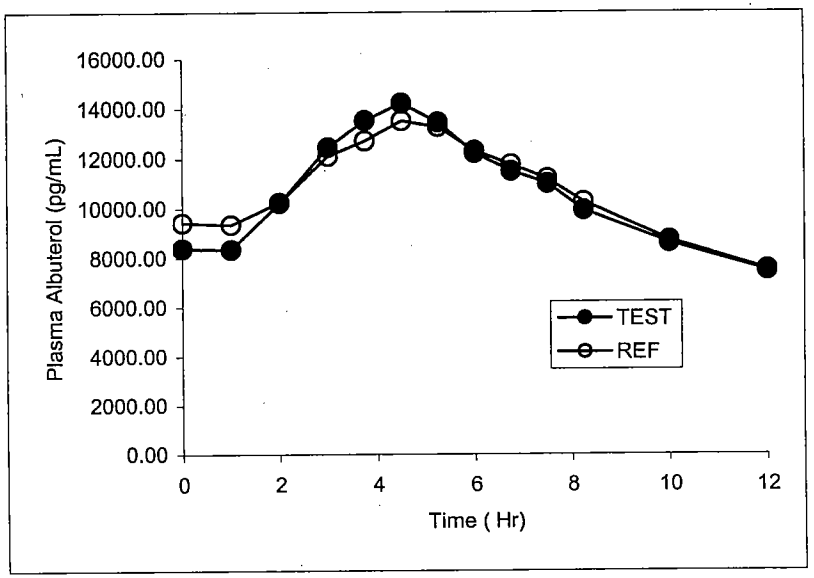

Table 11: Individual Parameter Values (Steady-State Study #2398, ANDA 76130, N = 36)

											TEST/REF						
SUB	SEQ	TRT	AUC(0-t)	CMAX	CSSAV	CMIN	TMAX	FLUC1	FLUC2		AUC(0-t)	CMAX	CSSAV	CMIN	TMAX	FLUC1	FLUC2
1	2	A	107307	11418.8	8942.2	6663.4	4.5	53.2	71.4		1.07	0.83	1.07	1.33	1.00	0.51	0.41
2	1	A	98554	12587.2	8212.9	4872.9	3.75	93.9	158.3		0.80	0.92	0.80	0.72	0.99	1.40	1.54
3	1	A	176894	22576.2	14741.2	10608.3	5.25	81.2	112.8		1.20	1.43	1.20	1.06	0.88	1.72	1.94
5	2	A	153397	19580.7	12783.1	8969.6	4.5	83	118.3		1.00	1.08	1.00	1.04	0.86	1.12	1.08
6	1	A	91391	10608.7	7615.9	5428.9	3.75	68	95.4		0.95	0.81	0.95	0.87	0.83	0.79	0.86
7	1	A	79292	10306	6607.6	3847.6	4.5	97.7	167.9		0.96	0.94	0.96	0.81	1.20	1.09	1.29
8	1	A	68421	9034.1	5701.8	2934.5	3.75	107	207.9		0.72	0.63	0.72	0.58	0.83	0.92	1.14
9	2	A	137316	16297.1	11443	7676.6	3.75	75.3	112.3		0.93	1.02	0.93	0.91	0.83	1.22	1.24
10	1	A	170119	18153.7	14176.5	9149.1	6	63.5	98.4		0.98	0.98	0.98	0.95	1.60	1.04	1.07
11	2	A	145554	15470.6	12129.5	8698.5	5.25	55.8	77.9		0.87	0.91	0.87	0.88	1.00	1.07	1.06
12	1	A	118584	14570	9882	5584.9	5.25	90.9	160.9		1.05	1.09	1.05	0.94	1.00	1.15	1.27
13	2	A	112191	15960.6	9349.2	7310.1	3	92.5	118.3		1.07	1.28	1.07	1.14	1.00	1.34	1.26
14	1	A	115848	14536.9	9654	6371.8	3	84.6	128.1		1.19	1.09	1.19	1.19	1.50	0.86	0.87
15	1	A	177215	19895.4	14767.9	11788.8	3	54.9	68.8		1.03	1.00	1.03	1.11	0.80	0.84	0.79
16	2	A	119983	13616.2	9998.6	7178.1	3	64.4	89.7		1.30	1.27	1.30	1.34	1.00	0.93	0.90
17	2	A	164288	18715.2	13690.7	10655.7	3.75	58.9	75.6		1.14	1.05	1.14	1.16	0.83	0.81	0.79
18	2	A	122441	17423.2	10203.4	6903.7	3.75	103.1	152.4		0.99	1.13	0.99	1.04	0.83	1.22	1.16
20	1	A	151969	17231.6	12664.1	9319.7	5.25	62.5	84.9		1.16	1.26	1.16	1.12	0.78	1.26	1.30
21	2	A	108209	13227.6	9017.4	6914.7	4.5	70	91.3		0.94	1.03	0.94	1.04	0.86	1.10	0.99
22	1	A	160880	19057.2	13406.6	8428.8	3	79.3	126.1		1.10	1.08	1.10	1.14	1.00	0.94	0.91
23	2	A	111143	11898.5	9261.9	7155.5	6.18	51.2	66.3		0.87	0.84	0.87	0.96	2.06	0.80	0.73
24	2	A	130043	16285.8	10836.9	7789.9	4.5	78.4	109.1		0.90	0.88	0.90	0.88	1.00	0.98	1.01
25	2	A	114720	13907.1	9560	7247.8	4.5	69.7	91.9		0.81	0.80	0.81	0.89	0.86	0.89	0.81
26	1	A	150967	19858.8	12580.6	9685.4	3.75	80.9	105		1.08	1.27	1.08	1.15	0.83	1.32	1.24
28	2	A	84817	11938.7	7068.1	5025.8	5.25	97.8	137.5		0.88	0.90	0.88	0.95	1.17	0.99	0.91
29	1	A	125380	19196.6	10448.3	6510.2	3	121.4	194.9		1.27	2.05	1.27	0.92	0.40	4.29	5.89
30	2	A	134799	15879.8	11233.3	8430.7	4.5	66.3	88.4		0.93	0.95	0.93	1.06	1.00	0.92	0.80
32	1	A	90283	11139.3	7523.6	5305.1	5.25	77.5	110		1.06	1.30	1.06	1.09	1.00	1.50	1.45
33	2	A	144470	18284.5	12039.2	8060.1	3.75	84.9	126.9		1.10	1.15	1.10	1.04	1.00	1.14	1.19
35	2	A	145462	17797.2	12121.8	9733.8	4.5	66.5	82.8		0.92	1.05	0.92	0.93	0.86	1.35	1.34
37	1	A	102316	16721.5	8526.4	6238.2	4.5	123	168.1			1.68			1.00		
38	2	A	125367	15227.2	10447.2	7817.2	3	70.9	94.8		0.88	0.91	0.88	0.89	0.67	1.05	1.04
42	1	A	128377	15656.9	10698.1	6994.7	4.5	81	123.8		0.77	0.82	0.77	0.84	1.50	1.04	0.95
43	1	A	121963	15237.5	10163.6	6949.9	4.5	81.5	119.2		1.19	1.43	1.19	1.00	0.86	1.89	2.26
44	2	A	124529	14730	10377.4	7296.3	4.5	71.6	101.9		0.90	0.87	0.90	0.86	0.86	0.98	1.02
46	1	A	138438	15019.6	11536.5	9103.9	5.25	51.3	65		0.97	0.97	0.97	1.16	0.70	0.80	0.67
		Mean	**126470.19**	**15529.06**	**10539.18**	**7462.51**	**4.28**	**78.16**	**113.95**	**# #**	**1.00**	**1.08**	**1.00**	**1.00**	**0.98**	**1.18**	**1.23**
		%CV	**21.46**	**20.31**	**21.46**	**25.66**	**20.71**	**23.31**	**31.35**	**# #**	**14.15**	**25.11**	**14.15**	**15.78**	**29.76**	**51.35**	**71.32**

1	2	B	100505	13694.9	8375.4	5015.4	4.5	103.6	173.1
2	1	B	123743	13629.2	10311.9	6730.8	3.8	66.9	102.5
3	1	B	147768	15774.9	12314	9979.2	6	47.1	58.1
5	2	B	153761	18112.6	12813.5	8650.6	5.25	73.8	109.4
6	1	B	96216	13088	8018	6209.1	4.5	85.8	110.8
7	1	B	82772	10946.7	6897.7	4755	3.75	89.8	130.2
8	1	B	95477	14295.3	7956.4	5064.5	4.5	116	182.3
9	2	B	147986	16026.6	12332.2	8397	4.5	61.9	90.9
10	1	B	174287	18496.5	14523.9	9639.7	3.75	61	91.9
11	2	B	166771	17094.4	13897.6	9859.8	5.25	52.1	73.4
12	1	B	113283	13390.1	9440.2	5911.4	5.25	79.2	126.5
13	2	B	105147	12439.4	8762.2	6406.8	3	68.8	94.2
14	1	B	97299	13309.8	8108.2	5369	2	97.9	147.9
15	1	B	171827	19926.4	14318.9	10620.8	3.75	65	87.6
16	2	B	92354	10703.2	7696.1	5370.3	3	69.3	99.3
17	2	B	143888	17890.5	11990.7	9160.1	4.5	72.8	95.3
18	2	B	123700	15394.5	10308.4	6650.6	4.5	84.8	131.5
20	1	B	131552	13724.8	10962.6	8296	6.75	49.5	65.4
21	2	B	115326	12815.2	9610.5	6678.9	5.25	63.9	91.9
22	1	B	146253	17712.6	12187.8	7408.5	3	84.5	139.1
23	2	B	127776	14242.4	10648	7460.8	3	63.7	90.9
24	2	B	144352	18480.1	12029.3	8872.7	4.5	79.9	108.3
25	2	B	141779	17388.9	11815	8164.8	5.25	78.1	113
26	1	B	139585	15596.6	11632.1	8446.3	4.5	61.5	84.7
28	2	B	96911	13218.3	8076	5277.9	4.5	98.3	150.4
29	1	B	98663	9374.1	8221.9	7045.1	7.5	28.3	33.1
30	2	B	145517	16707.7	12126.4	7937.1	4.5	72.3	110.5
32	1	B	85461	8550.4	7121.7	4866.9	5.25	51.7	75.7
33	2	B	131615	15918.7	10967.9	7721.6	3.75	74.7	106.2
35	2	B	158386	16954	13198.8	10472.9	5.25	49.1	61.9
37	1	B	.	9976.6	.	.	4.5	.	.
38	2	B	141772	16756.7	11814.3	8772.5	4.5	67.6	91
42	1	B	165817	19093.9	13818.1	8290.3	3	78.2	130.3
43	1	B	102441	10653.5	8536.7	6978	5.25	43.1	52.7
44	2	B	138625	16889.1	11552.1	8457.8	5.25	73	99.7
46	1	B	142671	15468	11889.2	7874	7.45	63.9	96.4
		Mean	**128322.46**	**14825.96**	**10693.53**	**7508.92**	**4.58**	**70.77**	**103.03**
		%CV	**20.58**	**19.70**	**20.58**	**22.33**	**26.15**	**25.56**	**31.38**

Table 12: Parametric Data (ANDA 76-130, Steady-State Study 2398, N=36)

Parameter	TEST (A)		REF (B)		A/B	90%- CI	ISV
	Mean	%CV	Mean	%CV			
AUC	126470.2	21.5	128322.5	20.6	**0.99**	**94.89-102.99**	9.34%
(ng/mL*hr)	*126470.10*		*127519.20*		***0.99***		
Cmax	15529.1	20.3	14826.0	19.7	**1.05**	**98.31-110.85**	14.43%
(ng/mL*hr)	*15529.10*		*14825.90*		***1.05***		
CssAVe (ng/mL)	10539.2	21.5	10693.5	20.6	**0.99**		
Cmin (ng/mL)	7462.5	25.7	7508.9	22.3	**0.99**		
Tmax (hr)	4.3	20.7	4.6	26.1	**0.93**		
FLUC1 (%)	78.16	23.3	70.77	25.6	**1.10**		
FLUC2 (%)	114.0	31.3	103.0	31.4	**1.11**		

Data given in italics are based on LS means
ISV = Intrasubject Variability
All data are based on the reviewer's calculations
The 90% confidence interval are based on the log-transformed data

Albuterol Sulfate

Extended release tablets, 8-mg, 4-mg
ANDA # 76-130
Reviewer: Gur J.P. Singh
File #7613A.701

Sidmak Labs

17West Street
East Hanover, NJ 07936
Submission Dates:
July 19 and August 3 ~~& 7, 2001~~ (5)

Review of Amendments

On March 2, 2001, the sponsor submitted single dose bioequivalence studies conducted under fasting and non-fasting conditions, and a multiple dose study on its albuterol sulfate 8-mg tablet, and a fasting study on albuterol sulfate 4-mg extended release tablet. The application also contained dissolution data for these drug products. A review of that submission was completed on June 14, 2001, and the firm was informed (Letter date: June 20, 2001) of the following deficiency:

> *The dissolution testing on your albuterol sulfate 4-mg and 8-mg tablets is unacceptable. You should conduct dissolution testing on 12 units of test and reference products using the USP apparatus II (Paddle, 50 rpm) in different dissolution media (e.g., water, 0.1N HCl and buffers at pH 4.5 and 6.8). You may refer to the following Agency Guidances:*
>
> *Bioavailability and bioequivalence studies for orally administered drug products – General Considerations (10/2000)*
>
> *Extended release oral dosage forms: Development, evaluation and application of in vitro-in vivo correlations (9/1997)*

In the current amendments the firm submitted the requested information. A summary of the information is as follows:

> ***Method:*** Dissolution testing was performed using the USP apparatus II (paddle) operated at 50 rpm in four media: (1) water, (2) 0.1N HCl, (3) pH 4.5 buffer (Phosphate), and (4) pH 6.5 buffer (Phosphate) .
>
> ***Test and reference products:*** *Lots* of the test and reference products used for dissolution testing and the bioequivalence study were identical (see the table blow for lot numbers)
>
> ***Results:*** Dissolution data are listed below

In vitro Dissolution Testing (FDA Suggested Method)

Drug Product: Albuterol Sulfate Tablets
Dose Strength: 4 mg and 8 mg

ANDA # 76-130, the raw data are given in vol. 2.1
Firm: **Sidmak Laboratories**
Submission Date: July 19 & August 3 &7, 2001
File # **76130A.701**

Conditions of Dissolution Testing:

USP Apparatus II Paddle, RPM: 50
Units Tested: 12
Media: Four media (see below)
Specifications: Not established

Reference Drug: Volmax^{R} 4-mg and 8-mg tablets

Results of Dissolution Testing:

F_2 Values (4 vs. 8 mg)		
Product	Medium	F_2
TEST	Water	59.16
	0.1 N HCl	55.88
	pH 4.5	70.31
	pH6.8	55.22
REF	Water	66.44
	0.1 N HCl	71.19
	pH 4.5	67.07
	pH6.8	55.10

TEST vs. REF		
4 mg	Water	59.50
	0.1 N HCl	62.30
	pH 4.5	42.88
	pH6.8	49.30
8 mg	Water	74.80
	0.1 N HCl	63.29
	pH 4.5	60.28
	pH6.8	49.85

A. Media = Water

Sampling Time (Hr)	Test Product (T) Lot # 00-039T Strength: **4mg**			Reference Product (R) Lot # D12099 Strength: **4 mg**			T/R
	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV	
1	2		27.4	13		12.4	**0.15**
2	24		13.4	27		10.7	**0.89**
4	56		5.1	55		10.1	**1.02**
6	74		3.2	81		8.2	**0.91**
8	86		2.3	91		2.6	**0.95**
10	92		1.4	94		1.7	**0.98**

Sampling Time	Test Product (T) Lot # 00-016T	Reference Product (R) Lot # D004184	T/R

(Hr)	Strength: **8mg**			Strength: **8 mg**			
	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV	
1	9		32.2	13		8.6	**0.69**
2	32		6.3	33		9.9	**0.97**
4	62		3.6	62		8.1	**1.00**
6	80		2.8	85		6.1	**0.94**
8	91		2.2	93		4.2	**0.98**
10	96		1.7	95		4.9	**1.01**

B. Media = 0.1 N HCl

Sampling Time (Hr)	Test Product (T) Lot # 00-039T Strength: **4mg**			Reference Product (R) Lot # D12099 Strength: **4 mg**			**T/R**
	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV	
1	3		19.8	11		15.0	**0.27**
2	19		30.2	24		7.6	**0.79**
4	56		3.8	49		6.5	**1.14**
6	75		2.3	72		7.3	**1.04**
8	87		1.7	90		3.2	**0.97**
10	93		2.2'	95		2.1	**0.98**

Sampling Time (Hr)	Test Product (T) Lot # 00-016T Strength: **8mg**			Reference Product (R) Lot # D004184 Strength: **8 mg**			**T/R**
	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV	
1	7		38.8	11		16.2	**0.64**
2	32		7.5	26		11.1	**1.23**
4	63		4.2	54		8.5	**1.17**
6	81		3.0	78		7.2	**1.04**
8	91		2.2	91		5.0	**1.00**
10	97		1.6	95		6.6	**1.02**

C. Media = pH 4.5 buffer

Sampling Time (Hr)	Test Product (T) Lot # 00-039T Strength: **4mg**	Reference Product (R) Lot # D12099 Strength: **4 mg**	**T/R**

	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV	
1	2		28.3	14		8.6	**0.14**
2	21		34.8	32		10.8	**0.66**
4	52		4.5	64		10.7	**0.81**
6	71		2.4	89		11.2	**0.80**
8	83		1.5	98		4.2	**0.85**
10	91		1.4	99		2.5	**0.92**

Sampling Time (Hr)	Test Product (T) Lot # 00-016T Strength: **8mg**			Reference Product (R) Lot # D004184 Strength: **8 mg**			**T/R**
	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV	
1	5		55.2	13		12.9	**0.38**
2	27		8.1	30		12.6	**0.90**
4	55		4.1	59		10.9	**0.93**
6	74		3.1	82		8.2	**0.90**
8	86		2.3	92		3.1	**0.93**
10	94		1.7	95		2.3	**0.99**

D. Media = pH 6.8 buffer

Sampling Time (Hr)	Test Product (T) Lot # 00-039T Strength: **4mg**			Reference Product (R) Lot # D12099 Strength: **4 mg**			**T/R**
	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV	
1	1		25.6	11		8.7	**0.09**
2	6		56.0	23		8.7	**0.26**
4	42		6.0	46		9.2	**0.91**
6	62		3.6	68		11.4	**0.91**
8	75		2.6	87		5.7	**0.86**
10	85		2.3	92		2.7	**0.92**

Sampling Time (Hr)	Test Product (T) Lot # 00-016T Strength: **8mg**			Reference Product (R) Lot # D004184 Strength: **8 mg**			**T/R**
	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV	
1	2	—	54.6	12	—	12.8	**0.17**

2	22		11.9	27		12.3	**0.81**
4	49		5.2	57		9.5	**0.86**
6	67		3.9	80		6.3	**0.84**
8	80		3.2	92		2.7	**0.87**
10	88		2.3	96		2.8	**0.92**

Comments

1. The firm has conducted in vitro dissolution in four media in response to the Agency's request of June 20, 2001. Based on the data submitted by the firm:

   The in vitro dissolution testing should be conducted in de-ionized water using USP apparatus 2 (paddle) at 50 rpm. The dissolution testing should meet the following specifications:

Time (Hr)	% Dissolution
2	—
4	—
6	—
8	NLT —

   The above represents the Agency's interim recommendation for dissolution testing. Final recommendations will be made upon review of dissolution data for three commercial lots.

2. For future in vitro dissolution testing on extended-release drug products, the firm should note that the phosphate buffer is not appropriate for pH 4.5.

Recommendations

The in vitro dissolution testing conducted by Sidmak Laboratories on its albuterol sulfate 8-mg and 4-mg tablets is acceptable. Dissolution testing should be incorporated into the firm's manufacturing and quality control programs. The in vitro dissolution testing should be conducted in de-ionized water using USP apparatus 2 (paddle) at 50 rpm. The dissolution testing should meet the following specifications:

Time (Hr)	% Dissolution
2	—
4	—
6	—

8 NLT —

The above represents the Agency's interim recommendation for dissolution testing. Final recommendations will be made upon review of dissolution data for three commercial lots.

For future in vitro dissolution testing on extended-release drug products, the firm should note that the phosphate buffer is not appropriate for pH 4.5.

The firm should be informed of above recommendations.

Based on the previous (June 14, 2001) review, the sponsor has submitted acceptable bioequivalence studies on its albuterol sulfate 4-mg and 8-mg tablets. Based on the data submitted hitherto, the firm has met requirements of in vivo bioequivalence and in vitro dissolution testing on its albuterol sulfate 4-mg and 8-mg tablets.

Gur J.P. Singh, Ph.D.
Review Branch II, Division of Bioequivalence.

8/8/2001

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR

CONCUR: Barbara M Davit DATE: 8/9/01

for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence.

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BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA/AADA: 76-130 APPLICANT: Sidmak Laboratories

DRUG PRODUCTS: Albuterol sulfate extended release tablets, 4 mg and 8 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that dissolution testing should be incorporated into the your manufacturing and quality control programs. The in vitro dissolution testing should be conducted in de-ionized water using USP apparatus 2 (paddle) at 50 rpm. The dissolution testing should meet the following specifications:

Time (Hr)	% Dissolution
2	—
4	—
6	—
8	NLT —

The above represents the Agency's interim recommendation for dissolution testing. Final recommendations will be made upon review of dissolution data for three commercial lots.

For future in vitro dissolution testing on extended-release drug products, please note that the phosphate buffer is not appropriate for pH 4.5.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Barbara M Savit

for Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA: 76-130
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD-655/Reviewer CDR 8/8/01
HFD-655/Bio Team Leader
HFD-617/Project Manager
for HFD-650/Dale Conner 8/9/01

8/8/01

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BIOEQUIVALENCY - ACCEPTABLE **Submission date: July 19, 2001**

✓ 1. **Study Amendment** (STA) Strength: 4 mg & 8 mg
Outcome: AC

BIOEQUIVALENCY - ACCEPTABLE **Submission date: August 3,2001**

✓ 2. **Study Amendment** (STA) Strength: 4 mg &8 mg
Outcome: AC

~~BIOEQUIVALENCY - ACCEPTABLE~~ **~~Submission date: August 7, 2001~~**

X 3. **Study Amendment** ~~(STA)~~ Strength: 4 mg & 8mg
~~Outcome:~~ AC

New Correspondence KS 8/20/01

WinBio Comments: The study amendments are acceptable.

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 76-130 **SPONSOR: Sidmak**

DRUG AND DOSAGE FORM: Albuterol Sulfate Extended-Release Tablets

STRENGTH (S): 4 mg and 8 mg

TYPES OF STUDIES: Single dose fasting Study, non-fasting and multiple-dose BE studies

CLINICAL STUDY AND SAMPLE ANAYSIS SITE (S): _____

STUDY SUMMARY: The in vivo bioequivalence studies are acceptable.
DISSOLUTION: Acceptable
WAIVER: N/A

DSI INSPECTION STATUS

Inspection needed: **No**	Inspection status: N/A	Inspection results: N/A
First Generic: **YES** New facility __No___ For cause __No___ Other _None__		

PRIMARY REVIEWER: (Gur J.P. Singh, Ph.D.) BRANCH: II

INITIAL: GJPS DATE: 8/8/01

TEAM LEADER: (Shriniwas Nerurkar, Ph.D.) BRANCH: II

INITIAL: _____ DATE: 8/9/2001

for DIRECTOR, DIVISION OF BIOEQUIVALENCE : Dale P. Conner, Pharm. D.

INITIAL: BMS DATE: 8/9/01

Albuterol Sulfate

Extended release tablets, 8-mg, 4-mg
ANDA # 76-130
Reviewer: Gur J.P. Singh

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Sidmak Labs

17West Street
East Hanover, NJ 07936
Submission Dates:
December 14, 2001 & March 5, 2002

Review of Two Amendments

(Requests for a pre-approval change in dissolution specifications)

On March 2, 2001, the sponsor submitted single dose bioequivalence studies conducted under fasting and non-fasting conditions, and a multiple dose study on its albuterol sulfate 8-mg tablet, and a fasting study on albuterol sulfate 4-mg extended release tablet. The application also contained dissolution data for these drug products. A review of that submission was completed on June 14, 2001, and the firm was informed (Letter date: June 20, 2001) of deficiencies in dissolution data.

The firm submitted its response to the deficiencies in dissolution testing on July 19 and August 3 &7, 2001. A review of dissolution data was completed on August 9, 2001 and the firm was advised as follows:

> *Please note that dissolution testing should be incorporated into the your manufacturing and quality control programs. The in vitro dissolution testing should be conducted in de-ionized water using USP apparatus 2 (paddle) at 50 rpm. The dissolution testing should meet the following specifications:*
>
> | *Time (Hr)* | *% Dissolution* |
> |---|---|
> | *2* | —— |
> | *4* | —— |
> | *6* | —— |
> | *8* | *NLT* — |
>
> *The above represents the Agency's interim recommendation for dissolution testing. Final recommendations will be made upon review of dissolution data for three commercial lots.*
>
> *For future in vitro dissolution testing on extended-release drug products, please note that the phosphate buffer is not appropriate for pH 4.5.*

In the current amendment, the firm has requested a pre-approval change in dissolution specifications for its albuterol 4-mg and 8-mg tablets. The basis of the request is inability of one commercial lot of each of the 4-mg and 8-mg tablets to meet the lower limits of dissolution ranges proposed in the

application, due to certain level of variation in dissolution at the 6th hour time point. The firm has not submitted dissolution data to indicate observed level of variation.

Based on the two amendments, the firm has the following two sets of its " previously submitted and proposed" dissolution specifications:

1. ***March 5, 2002 amendment***

Time	Previously Submitted		Proposed	
(Hr)	4-mg Tablet	8-mg tablet	4-mg Tablet	8-mg tablet
4				
6				
10				

2. ***December 14, 2001 amendment***

Time	Previously Submitted		Proposed	
(Hr)	4-mg Tablet	8-mg tablet	4-mg Tablet	8-mg tablet
4				
6				
10				

Comments

1. Based on the August 9, 2001, review the firm was provided the following dissolution specifications:

Time (Hr)	% Dissolution
2	—
4	—
6	—
8	NLT —

The Agency's specifications were the same for both the 4-mg and 8-mg tablets. The firm is requesting separate dissolution specifications for these products and the requested specifications are different in the two amendments. It has not provided justification for different dissolution specifications.

Furthermore, the Agency's specifications included % dissolution determination at 2, 4, 6 and 8 hours, whereas the firm's proposal is based dissolution at 4, 6 and 10 hours.

3. Based on the March 5, 2002 amendment, dissolution time points for the ANDA stability study and QC release are 1, 2, 4, 6, 8 and hours, and 2, 6, and 10 hours respectively. Time points selected for dissolution testing should be the same for ANDA related studies and QC release.

2. The sponsor was informed that the recommended dissolution specifications were provided on an interim basis; final recommendation would be made upon review of dissolution data for three commercial lots. The firm has not submitted the requested three-lot data. In the absence of the data, the Agency cannot revise its recommendation for the interim dissolution specifications.

Recommendation

The sponsor's request for pre-approval changes in dissolution specifications is denied due to the above comments.

Gur J.P. Singh, Ph.D.
Review Branch II
Division of Bioequivalence.

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR 4/25/2002

CONCUR: for Dale P. Conner, Pharm.D. DATE: 5/8/2002
Director
Division of Bioequivalence.

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BIOEQUIVALENCY DEFIENCY TO BE PROVIDED TO THE APPLICANT

ANDA/AADA: 76-130 APPLICANT: Sidmak Laboratories

DRUG PRODUCTS: Albuterol sulfate extended release tablets, 4 & 8 mg

The Division of Bioequivalence has completed its review and it has identified the following deficiencies.

You were previously provided with the following dissolution specifications.

Time (Hr)	% Dissolution
2	———
4	———
6	———
8	NLT —

The Agency's specifications were the same for both the 4-mg and 8-mg tablets. You are requesting separate dissolution specifications for these products. Furthermore your proposed specifications are different based on the December 14, 2001 March 5, 2002 amendments. Please provide justification for different dissolution specifications for the 4-mg and 8-mg product.

It is also noted that the Agency's specifications included % dissolution determination at 2, 4, 6 and 8 hours, whereas the your proposal is based dissolution at 4, 6 and 10 hours.

Based on the March 5, 2002 amendment, dissolution time points for the ANDA stability study and QC release are 1, 2, 4, 6, 8 and hours, and 2, 6, and 10 hours respectively. Time points selected for dissolution testing should be the same for ANDA related studies and QC release. You are requested to use the time points mentioned in the specifications outlined above.

You were informed that the above dissolution specifications were provided on an interim basis, final recommendation would be made upon review of dissolution data for three commercial lots. You have not submitted the requested three-lot data. In the absence of the data, the Agency cannot revise its recommendation for the interim dissolution specifications.

Sincerely yours,

for

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA: 76-130
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD-655/Reviewer GDR 4-24-02
HFD-655/Bio Team Leader
HFD-617/Project Manager
HFD-650/Dale Conner for RWL 5/8/2002

4/25/02

V:\FIRMSNZ\SIDMAK\LTRS&REV\76130A1201.doc

BIOEQUIVALENCY - DEFICIENCY **Submission date: Dec. 14, 2001**

1. **Study Amendment** (STA) Strength: 4 mg & 8 mg
✓ **Outcome:** IC

BIOEQUIVALENCY - DEFICIENCY **Submission date: March 5, 2002**

2. **Study Amendment** (STA) Strength: 4 mg & 8 mg
✓ **Outcome:** IC

WinBio Comments: The study amendments are incomplete.

APPEARS THIS WAY
ON ORIGINAL

Albuterol Sulfate

Extended release tablets, 8-mg, 4-mg
ANDA # 76-130
Reviewer: Gur J.P. Singh

File #V:\FIRMSNZ\SIDMAK\LTRS&REV\76130A502.doc

Sidmak Labs

17West Street
East Hanover, NJ 07936
Submission Dates:
May 21 and 31, 2001

Review of Two Amendments

The firm has previously submitted acceptable bioequivalence studies on its albuterol sulfate 8-mg and 4-mg tablets. It submitted dissolution data on July 19 and August 3 &7, 2001. A review of dissolution data was completed on August 9, 2001 and the firm was advised as follows:

> *Please note that dissolution testing should be incorporated into the your manufacturing and quality control programs. The in vitro dissolution testing should be conducted in de-ionized water using USP apparatus 2 (paddle) at 50 rpm. The dissolution testing should meet the following specifications:*
>
> | *Time (Hr)* | *% Dissolution* |
> |---|---|
> | *2* | — |
> | *4* | — |
> | *6* | — |
> | *8* | *NLT* — |
>
> *The above represents the Agency's interim recommendation for dissolution testing. Final recommendations will be made upon review of dissolution data for three commercial lots.*

2. In the current amendment, the firm indicates the above dissolution specifications are an issue, because neither the ANDA batches nor the reference listed drug meets the specifications. It has submitted data for dissolution testing in ———.

3. The firm also proposed separate dissolution specifications for its 4-mg and 8-mg tablets. To support their request the firm provided data for % dissolution in ———. It has also stated that the two strengths may have different dissolution specifications, because in vivo bioequivalence of the higher and lower strengths was based on separate in vivo studies.

Comments

1. Dissolution data submitted in the current amendment are different from those submitted on July 19 and August 3, based on which the Agency recommended the interim

specifications. Those data meet the Agency specifications.

2. Based on the July 19 and August 3, 2001 amendments, the Agency recommended dissolution testing in de-ionized water, not in [redacted]. If the sponsor wishes to submit additional dissolution data, it should be based on the recommended method (900 mL of de-ionized water, apparatus II (paddle at 50 rpm).

3. The firm's request for separate dissolution specifications for the 4-mg and 8-mg tablets is not acceptable, because

   The two products have similar formulations, even though they are not made from the same [redacted],

   The innovator product does not have separate dissolution specifications for the higher and lower strength product, and

   Both the 4-mg and 8-mg tablets of the test product meet Agency's specification, when dissolution testing was conducted in de-ionized water.

Recommendation

The sponsor should be informed of above comments.

Gur J.P. Singh, Ph.D.
Review Branch II
Division of Bioequivalence.

6/19/2002

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR

CONCUR: DATE: 6/19/02

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence.

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BIOEQUIVALENCY DEFIENCY TO BE PROVIDED TO THE APPLICANT

ANDA/AADA: 76-130 APPLICANT: Sidmak Laboratories

DRUG PRODUCTS: Albuterol sulfate extended release tablets, 4 & 8 mg

The Division of Bioequivalence has completed its review and it has identified the following deficiencies.

Your proposal for separate dissolution specifications for the 4-mg and 8-mg tablets is not acceptable, because (1) these two products have similar formulations and (2) based on the data submitted previously, both products meet the Agency's specification when dissolution was conducted in water. Based on those data, you were provided with the following dissolution specifications.

Time (Hr)	% Dissolution
2	———
4	———
6	———
8	NLT —

Dissolution data submitted in the current amendment (May 21, 2002) are different from those submitted on July 19 and August 3,2001, based on which the Agency recommended the interim specifications.

Based on the July 19 and August 3 amendments, the Agency recommended dissolution testing in de-ionized water, not in ———. If you wish to submit additional dissolution data, it should be based on the recommended method (900 mL of de-ionized water, apparatus II (paddle at 50 rpm).

You have been informed that the above dissolution specifications were provided on an interim basis, final recommendation would be made upon review of dissolution data for three commercial lots. You have not submitted the requested three-lot data. In the absence of the data, the Agency cannot revise its recommendation for the interim dissolution specifications.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA: 76-130
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD-655/Reviewer 5-15-02 6/19/02
HFD-655/Bio Team Leader
HFD-617/Project Manager
HFD-650/Dale Conner 6/19/02

V:\FIRMSNZ\SIDMAK\LTRS&REV\76130A502.doc

BIOEQUIVALENCY - DEFICIENCY **Submission date: May 21, 2002**

1. **Study Amendment** (STA) Strength: 4 mg & 8 mg
Outcome: IC

BIOEQUIVALENCY - DEFICIENCY **Submission date: May 31, 2002**

2. **Study Amendment** (STA) Strength: 4 mg & 8 mg
Outcome: IC

WinBio Comments: The study amendment is incomplete.

APPEARS THIS WAY
ON ORIGINAL

Albuterol Sulfate
Extended release tablets, 8-mg, 4-mg
ANDA # 76-130
Reviewer: Sikta Pradhan
File #76130A0602

Sidmak Labs
17West Street
East Hanover, NJ 07936
Submission Date:
June 21, 2002

REVIEW OF AN AMENDMENT

BACKGROUND

The firm had previously (submission dated March 2, 2001) conducted three acceptable in vivo bioequivalence studies under fasting, fed and multiple dosing conditions on its Albuterol Sulfate 8-mg ER tablets, and a fasting study on Albuterol Sulfate 4-mg ER tablets. The application also contained dissolution data for these drug products.

CURRENT SUBMISSION

Sidmak Laboratories, Inc. informed the Agency that the firm agrees to the interim specifications (listed below) for dissolution testing of the 8-mg and 4-mg Albuterol Sulfate tablets as recommended by the Division of Bioequivalence. Sidmak has further stated that firm has adopted these specifications for its product and as requested in the Agency letter, the firm has revised its finished product release and stability dissolution specifications/methods to reflect 900 mL of de-ionized water, apparatus 2 (paddle) at 50 rpm. The interim specifications for both strengths of this product are as follows:

2 nd hour	[redacted]
4 th hour	[redacted]
6 th hour	[redacted]
8 th hour	NLT [redacted]

RECOMMENDATION

Sidmak's acceptance of Agency recommendation on dissolution specifications has been acknowledged. Hence, no further action is needed on this submission.

Sikta Pradhan, Ph. D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG

7/22/2002

Concur: ---------- Date: 7/23/2002

for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA #76130A0602 (original), HFD-650 (Director), HFD-652 (Huang, Pradhan), Drug File, Division File

Draft: 7/10/02 Final: 7/21/02

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 76-130 SPONSOR: Sidmak

DRUG AND DOSAGE FORM: Albuterol Sulfate Extended-Release Tablets
STRENGTH (S): 4 mg and 8 mg
TYPES OF STUDIES: Single dose fasting Study, non-fasting and multiple-dose BE studies
CLINICAL STUDY AND SAMPLE ANAYSIS SITE (S): ———————

STUDY SUMMARY: The in vivo bioequivalence studies are acceptable.
DISSOLUTION: Acceptable
WAIVER: N/A

DSI INSPECTION STATUS

Inspection needed: **No**	Inspection status: N/A	Inspection results: N/A
First Generic: **YES** New facility __No__ For cause __No__ Other _None__		

PRIMARY REVIEWER : Sikta Pradhan BRANCH : I
INITIAL : Sikta Pradhan DATE : 7/21/02

TEAM LEADER : Yih-Chain Huang BRANCH : I
INITIAL : YCH DATE : 7/22/2002

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.
INITIAL : for DPC DATE : 7/23/2002

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA # 76-130 APPLICANT: Sidmak Laboratories, Inc.

DRUG PRODUCTS: Albuterol sulfate extended release tablets, 4 mg and 8 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

Your acceptance of Agency recommendation on dissolution specifications has been acknowledged.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

The in vitro dissolution testing should be conducted in 900 mL de-ionized water using USP apparatus 2 (paddle) at 50 rpm. The dissolution testing should meet the following interim specifications:

Time (Hr)	% Dissolution
2	———
4	———
6	———
8	NLT —

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

for Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA: 76-130
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Final with Dates)
HFD-652/ S. Pradhan
HFD-650/ Y. Huang 7/22/2002
HFD-617/ K. Scardina 7/23/02
HFD-650/ D. Conner for 7/23/2002

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BIOEQUIVALENCY - ACCEPTABLE **Submission date: June 21,2002**

1. **Study Amendment** (STA) ok Strength: 4 mg & 8 mg
Outcome: AC

Outcome Decisions: AC -Accepable

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 76-130 SPONSOR: Sidmak

DRUG AND DOSAGE FORM: Albuterol Sulfate Extended-Release Tablets
STRENGTH (S): 4 mg and 8 mg
TYPES OF STUDIES: Single dose fasting Study, non-fasting and multiple-dose BE studies
CLINICAL STUDY AND SAMPLE ANAYSIS SITE (S): ———————

STUDY SUMMARY: The in vivo bioequivalence studies are acceptable.
DISSOLUTION: Acceptable
WAIVER: N/A

DSI INSPECTION STATUS

Inspection needed: No	Inspection status: N/A	Inspection results: N/A
First Generic: YES New facility __No__ For cause __No__ Other _None__		

PRIMARY REVIEWER : Sikta Pradhan BRANCH : I
INITIAL : Sikta Pradhan DATE : 7/21/02

TEAM LEADER : Yih-Chain Huang BRANCH : I
INITIAL : YCH DATE : 7/22/2002

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.
INITIAL : DPC DATE : 7/23/2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-130

ADMINISTRATIVE DOCUMENTS

M E M O R A N D U M

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

DATE : March 9, 2001

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615) 09-MAR-2001

SUBJECT: Examination of the bioequivalence study and request for waiver submitted with an ANDA for Albuterol Sulfate Extended-release Tablets, 4 mg and 8 mg to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to USC 355 (j)(5)(B)(iv).

Sidmak Laboratories, Inc. has submitted ANDA 76-130 for Albuterol Sulfate Extended-release Tablets, 4 mg and 8 mg. The ANDA contains a certification pursuant to 21 USC 355 (j)(2)(A)(vii)(iv) stating that patent(s) for the reference listed drug will not be infringed by the manufacturing or sale of the proposed product. Also it is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study and request for waiver are complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for study and request for waiver submitted by Sidmak on March 2, 2001 for its Albuterol Sulfate product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

In determining whether a bio study is "complete" to satisfy statutory requirements, the following items are examined:

1. Study design

   (a) Appropriate number of subjects
   (b) Description of methodology

2. Study results

   (a) Individual and mean data is provided
   (b) Individual demographic data
   (c) Clinical summary

The issue raised in the current situation revolves around whether the study can purport to demonstrate bioequivalence to the listed drug.

We would appreciate a cursory review and your answers to the above questions as soon as possible so we may take action on this application.

DIVISION OF BIOEQUIVALENCE:

✓ Study meets statutory requirements

_____ Study does **NOT** meet statutory requirements

Reason:

✓ Waiver meets statutory requirements

_____ Waiver does **NOT** meet statutory requirements

Reason:

Michael H. Malinowski 3/14/01

Concur: Barbara M. Davit 3/15/01

for Director, Division of Bioequivalence

3/19/2001
Date

BIOEQUIVALENCE CHECKLIST FOR APPLICATION COMPLETENESS

ANDA 76-130 DRUG NAME Albuterol SO4 FIRM Sidmak Labs

DOSAGE FORM(s) ER Tabs, 4, 8mg

	YES	NO	REQUIRED AMOUNT	AMOUNT SENT	COMMENTS
Protocol	✓				
Assay Methodology	✓				
Procedure SOP	✓				
Methods Validation	✓				
Study Results Ln/Lin	✓				
Adverse Events	✓				
IRB Approval	✓				
Dissolution Data	✓				
Pre-screening of patients	✓				
Chromatograms	✓				
Consent forms	✓				
Composition	✓				
Summary of study	✓				
Individual Data & Graphs , Linear & (Ln)	✓				
PK/PD data disk	✓				
Randomization Schedule	✓				
Protocol Deviations	✓				

	YES	NO	REQUIRED AMOUNT	AMOUNT SENT	COMMENTS
Clinical site	✓				
Analytical site	✓				
Study investigators	✓				
Medical Records	✓	XXX			only for one study
Clinical Raw Data	✓				
Test Article Inventory	✓				
BIO Batch Size	✓				
Assay of active content drug	✓				
Content uniformity	✓				
Date of manufacture		X			
Exp. Date RLD	✓				
Biostudy lot numbers	✓				
Statistics	✓				
Summary results provided by the firm indicate studies pass BE criteria	✓				
Waiver requests for other strengths / supporting data	✓				

Additional comments:

Bio reviewer may need to request additional medical records.

Recommendation: COMPLETE / INCOMPLETE

Concur: Barbara M. Daniel 3/15/01
TZ, Br III

Reviewed by Mona M. Malone

_____ Date _____

Revised 6/7/2000

APPEARS THIS WAY
ON ORIGINAL

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-130 Applicant Sidmak Laboratories, Inc.
Drug Cellcept Extended-Release Tablets Strength 4mg, 8mg

APPROVAL ☑ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER:

1. Project Manager K Shenouda
   Review Support Br

DRAFT RECEIPT
Date 12/28/01
Initials [illegible]

FINAL ACTION
Date 8/19/02
Initials AP

Application Summary:
Original Rec'd date 3/5/01
Date Acceptable for Filing 3/5/01
Patent Certification (type) 1V
Date Patent/Exclus.expires 6/14/05, 10/11/05
Citizens Petition/Legal Case Yes ☐ No ☑
(If YES, attach email from PM to CP coord)
First Generic Yes ☒ No ☐
(If YES, check PETS)
Pediatric Exclusivity Tracking PETS)
Date checked 2/11/02 NDA# 19-604
Nothing Submitted 8/6/02 ☑
Written request issued ☐
Study Submitted ☐

EER Status Pending ☐ Acceptable ☑ OAI ☐
Date of EER Status 4/12/01
Date of Office Bio Review ~~8/9/02~~ 7/23/02
Date of Labeling Approv. Sum 8/06/02
Date of Sterility Assur. App. N/A
Methods Val. Samples Pending Yes ☐ No ☑
30 Day Clock Start _____ End _____
Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☑ No ☐
Interim Dissol. Specs in AP Ltr: Yes ☑

Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def./N/A Minor issued ☐ Date _____
Comments:

2. Div. Dir./Deputy Dir.
   Chemistry Div. I or II
   Comments:

Date 8/20/02
Initials [illegible]

Date 8/21/02
Initials [illegible]

CMC satisfactory.

3. Frank Holcombe
   Assoc. Dir. For Chemistry
   Comments: (First generic drug review)

Date _____
Initials _____

Date 9/2/02
Initials [illegible]

SATISFACTORY

4. Pat Beers Block
   Supv., Review Support Branch
   EER Status:

Date _____
Initials _____

Date _____
Initials _____

Refer to DLPS review below. 9/26/2002

Bioequivalence sites:
Clinical site:
Inspection needed: ☐ yes ☐ no
Status: ☐acceptable ☐unacceptable ☐ pending
Date of status: _____
Reason:

Analytical site:
Inspection needed: ☐ yes ☐ no
Status: ☐acceptable ☐unacceptable ☐pending
Date of status: _____
Reason:

Bioequivalence office level sign off:

Labeling Status:

Microbiology status:
Patent Certification:
Controlled Correspondence/Cit.Pet:
Comments: RLD =

REVIEWER:	DRAFT RECEIPT	FINAL ACTION
5. Greg Davis Supv., Reg. Support Branch	Date 9/26/02 Initials RW	Date 9/24/02 Per Letter Initials

Contains GDEA certification: Yes ☒ No ☐ Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92) Pediatric Exclusivity System
Patent/Exclusivity Certification: Yes ☒ No ☐ Date Checked 9/26/02
If Para. IV Certification- did applicant Para IV 4/2/01 Nothing Submitted ☒
Notify patent holder/NDA holder Yes ☒ No ☐ Written request issued ☐
Was applicant sued w/in 45 days: Yes ☐ No ☒ Study Submitted ☐
Has case been settled: Yes ☐ No ☐
Date settled: N/A
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☒ No ☐
Comments: RLD = Volmax Extended-release tablets 4mg + 8mg Muro Pharmaceutical, Inc. NDA 19-604
Sidmak made "paragraph IV" certifications to the '071, '049 and '229 patents. Sidmak was not sued within the 45-day period. There is no unexpired exclusivity. Sidmak is eligible for 180-day generic drug exclusivity.

6. Peter Rickman Acting Director, DLPS	Date 9/26/02 Initials RW	Date 9/26/02 Per Letter Initials

Comments: Acceptable (ES dated 4/2/01 (Verified 9/24/02). No O.A.I. alerts noted 6/8/01. Dissolution studies (fasting and non-fasting on 8mg, fasting on 4mg) found acceptable on 8/8/01. Bioequivalence studies (fasting and non-fasting on 8mg, fasting on 4mg) found acceptable on 8/8/01. Biostudies (dosing and analytical) performed by Office-Level Bio endorsed 8/19/01. Dissolution specifications finalized 7/22/02. Office-Level Bio endorsed 7/23/02. FPL found acceptable 7/16/02. CMC found acceptable 8/19/02. Methods validation completed and acceptable. First generic CMC audit completed.

7. Robert L. West Acting Deputy Director, OGD	Date 9/26/02 Initials RW	Date 9/26/02 Initials

Para.IV Patent Cert: Yes ☒ No ☐; Pending Legal Action: Yes ☐ No ☒; Petition: Yes ☐ No ☒
Comments: This "first generic" application is recommended for approval. As the first ANDA applicant with a "paragraph IV certification," Sidmak is eligible for 180-day generic drug exclusivity.

8. Gary Buehler Director, OGD	Date 9/26/02 Initials GB	Date 9/26/02 Initials GB

Comments:

First Generic Approval ☒ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

9. Project Manager Nicole Park Review Support Branch	Date Initials	Date 9/26/02 Initials

N/A Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
3:00p Time notified of approval by phone 3:39p Time approval letter faxed

FDA Notification:
9/26/02 Date e-mail message sent to "OGD approvals" account
9/26/02 Date Approval letter copied to "//cder/drugapp" directory

v:\reports\approval\approvrou

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-130

CORRESPONDENCE

Sidmak LABORATORIES, INC.

17 WEST STREET ● P.O. BOX 371 ● EAST HANOVER, NJ 07936 ● TELEPHONE: (201) 386-5566 ● (800) 922-0547

March 2, 2001

Office of Generic Drugs, CDER/FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: Abbreviated New Drug Application for Albuterol Sulfate Extended-release Tablets 4 mg and 8 mg

Dear Director, Office of Generic Drugs:

Sidmak Laboratories, Inc. submits today an original abbreviated new drug application ("ANDA") seeking approval to market Albuterol Sulfate Extended Release Tablets 4 mg and 8 mg, that are bioequivalent to the reference listed drug, Volmax® Tablets 4 mg and 8 mg marketed by Muro Pharmaceutical Inc., pursuant to NDA 19604.

This ANDA consists of the following:

Archival Copy	(Blue Folders, 15 Volumes)
Technical Review Copy - CMC	(Red Folders, 5 Volumes)
Technical Review Copy - Bioequivalence	(Orange Folders, 10 Volumes)

The four bioavailability/bioequivalence studies included in this submission are entitled:

Comparative, Single-Dose, Randomized, 2-Way Crossover Bioavailability Study of Sidmak and Muro (Volmax®) 8 mg Albuterol Sulfate Extended Release Tablets in Healthy Adult Males Under Fasting Conditions
Project No. 001466, 4 Volumes

Comparative, Randomized, Single-Dose, 3-Way Crossover Bioavailability Study of Sidmak and Muro (Volmax®) 8 mg Albuterol Sulfate Extended Release Tablets in Healthy Adult Males Under Fed and Fasted Conditions
Project No. 002397, 2 Volumes

Comparative, Randomized, 2-Way Crossover Steady State Bioavailability Study of Sidmak and Muro (Volmax®) 8 mg Albuterol Sulfate Extended Release Tablets in Healthy Adult Males Under Fasting Conditions
Project No. 002398, 2 Volumes

Comparative, Randomized, Single-Dose, 2-Way Crossover Bioavailability Study of Sidmak and Muro (Volmax®) 4 mg Albuterol Sulfate Extended Release Tablets in Healthy Adult Males Under Fasting Conditions
Project No. 002396, 2 Volumes

In the Technical Review Copy, we have included a diskette for each study, which contains the concentration and parameter data for that study. The information on each diskette is found in the file labeled "FDA.1". A hard copy of this data is also included in the review copy.

Two additional copies of the analytical methods and method validation are included with this submission, as Sidmak will use its stability indicating method for release and stability purposes.

Sidmak Laboratories, Inc. agrees to cooperate with the agency to resolve any method validation issues revealed during the method validation process after approval.

Included with this submission in Section III Patent Certification and Exclusivity is a Paragraph IV Certification for each of the patents listed. Sidmak Laboratories, upon receipt from FDA of an acknowledgement letter stating that this ANDA is sufficiently complete to permit a substantive review, will give the notice required by Section 505(j)(2)(B) of the FD&C Act and 21 CFR 314.95 to the patent holder.

For more detailed information on the organization of this ANDA, please refer to the Table of Contents. As a preface we are including an executive summary which briefly highlights the development of this ANDA.

Sidmak Laboratories, Inc. certifies that the field copy (Maroon Folders, 5 Volumes) of this application which has been forwarded to the New Jersey District Office, is a true copy of the technical section (21 CFR 314.94(a)(9)) contained in the archival and review copies of this abbreviated application.

Please direct any written communications regarding this ANDA to my attention at the above address. Should you have any questions regarding this submission please do not hesitate to contact Ms. Debbie Pakay at (973) 599-4353 or myself at (973) 599-4352.

Thank you for your prompt handling of this submission.

Respectfully submitted,

Roger W. Schwede
Vice President of Research and Development
and Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

ANDA 76-130

Sidmak Laboratories, Inc.
Attention: Roger W. Schwede
17 West Street
P.O. Box 371
East Hanover, NJ 07936

APR - 4

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Albuterol Sulfate Extended-release Tablets, 4 mg and 8 mg

DATE OF APPLICATION: March 2, 2001

DATE (RECEIVED) ACCEPTABLE FOR FILING: March 5, 2001

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative designated by the owner to receive the notice;

  2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a court order or judgement or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Gregg Davis, Chief, Regulatory Support Branch, at (301) 827-5862.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Michelle Dillahunt
Project Manager
(301) 827-5848

Sincerely yours,

Gregory S. Davis for

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 76-130
cc: DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/
Endorsement:
HFD-615/GDavis, Chief, RSB Davis 03-APR-2001 date
HFD-615/SMiddleton, CSO Smiddleton date 4/2/01
Word File V:\FIRMSNZ\SIDMAK\LTRS&REV\76130.ACK
F/T EEH 03/30/01
ANDA Acknowledgment Letter!

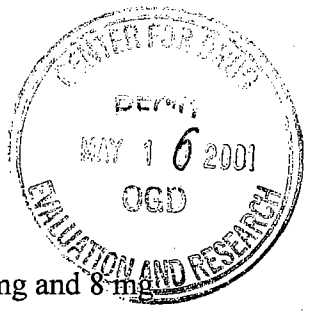
Sidmak LABORATORIES, INC.

17 WEST STREET ● P.O. BOX 371 ● EAST HANOVER, NJ 07936 ● TELEPHONE: (201) 386-5566 ● (800) 922-0547

NC

NEW CORRESP

May 15, 2001



Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Albuterol Sulfate Extended-release Tablets 4 mg and 8 mg
ANDA #76-130
PATENT AMENDMENT

Dear Sir/Madam:

Reference is made to the agency's communication dated 04/04/01 (copy attached). This letter has acknowledged the Paragraph IV patent certification and outlined the procedure for documentation of notification.

This amendment certifies that in accordance with 21 CFR 314.95(b), Sidmak Laboratories, Inc., hereby certifies that notice has been provided to each person identified under 21 CFR 314.95(a), and that the notice meets the content requirements under 21 CFR 314.95(c).

In accordance with 21 CFR 314.95(e), we are providing documentation of receipt of notice by providing the attached copies of the return receipt for each notice sent. Please note that there was an irregularity with the return receipt from Muro, in that the mail carrier neglected to indicate the delivery date on the receipt. According to the intranet inquiry performed at our attorneys request by the U.S. Post Office, the notice was delivered to Muro Pharmaceuticals on Friday, April 20, 2001. This was discussed with Mr. Robert West at OGD. At his suggestion, we are also including a copy of the letter sent to our attorney by ———————— attorneys for Muro, which states that they received the notice on April 20, 2001.

Should you have any questions or require any additional information, please do not hesitate to contact either Ms. Debbie Pakay at (973) 599-4353 or myself at (973) 599-4352.

Sincerely,

Roger Schwede
Vice President of R&D
and Regulatory Affairs

Enclosures: Copies of each return receipt for Muro and Alza
Intranet Inquiry from U.S. Post Office
Letter from [redacted]

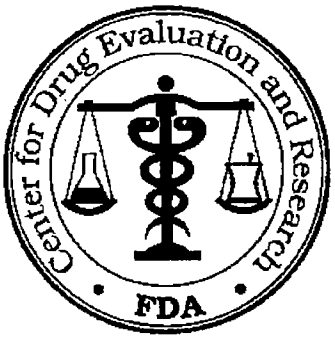
APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY AMENDMENT

ANDA 76-130

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

JUN 20 2001



TO: APPLICANT: Sidmak Labs

TEL: 973-386-5566 ext 4352

ATTN: Roger W. Schwede

FAX: 973-599-5721

FROM: Nina Nwaba

PROJECT MANAGER: 301-827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on March 2, 2001, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Albuterol Sulfate Extended Release Tablets, 8mg and 4mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 1 page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

jen

JUN 20 2001

BIOEQUIVALENCY DEFICIENCY

ANDA/AADA: 76-130 APPLICANT: Sidmak Laboratories

DRUG PRODUCTS: Albuterol sulfate extended release tablets, 4-mg and 8-mg

The Division of Bioequivalence has completed its review of submission (s) acknowledged on the cover sheet. The following deficiency has been identified.

The dissolution testing on your albuterol sulfate 4-mg and 8-mg tablets is unacceptable. You should conduct dissolution testing on 12 units of test and reference products using the USP apparatus II (Paddle, 50 rpm) in different dissolution media (e.g., water, 0.1N HCl and buffers at pH 4.5 and 6.8). You may refer to the following Agency Guidances:

Bioavailability and bioequivalence studies for orally administered drug products - General Considerations (10/2000)

Extended release oral dosage forms: Development, evaluation and application of in vitro-in vivo correlations (9/1997)

Sincerely yours,

for Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Gidmak®
LABORATORIES, INC.

17 WEST STREET ● P.O. BOX 371 ● EAST HANOVER, NJ 07936 ● TELEPHONE: (973) 386-5566 ● (800) 922-0547

NEW CORRESP

NC

June 22, 2001

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Albuterol Sulfate Extended-release Tablets 4 mg and 8 mg
ANDA #76-130 ***PATENT AMENDMENT***

Dear Sir/Madam:

Reference is made to the agency's communication dated 04/04/01 (copy attached). This letter has acknowledged the Paragraph IV patent certification and outlined the procedure for documentation of notification.

This amendment is submitted to notify the agency that no legal action was taken by each person provided notice as identified under 314.95(a) within the 45 day period.

We are providing documentation in the form of a letter from the Muro/ALZA attorney.

Should you have any questions or require any additional information, please do not hesitate to contact either Mr. Roger Schwede at (973) 599-4352 or myself at (973) 599-4353.

Sincerely,

Deborah L. Pakay
Manager, Regulatory Affairs

Enclosures: Letter from _____

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JUN 25 2001
OGD

Sidmak LABORATORIES, INC.

17 WEST STREET ● P.O. BOX 371 ● EAST HANOVER, NJ 07936 ● TELEPHONE: (973) 386-5566 ● (800) 922-0547

July 19, 2001

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AB

Re: Albuterol Sulfate Extended-release Tablets 4 mg and 8 mg
ANDA #76-130 ***BIOEQUIVALENCY AMENDMENT***

Dear Sir/Madam:

Reference is made to the agency's communication dated 06/20/01 (copy attached). This letter provided a deficiency in the dissolution testing submitted in the original application. We were asked to perform dissolution testing again (12 tablets of test and reference) in four different media using USP Apparatus II (Paddle, 50 rpm). Attached please find the following:

1) 4 mg - 12 tablet drug release (Sidmak vs. reference) in water
2) 4 mg - 12 tablet drug release (Sidmak vs. reference) in 0.1N HCl
3) 4 mg - 12 tablet drug release (Sidmak vs. reference) in pH 4.5 Buffer
4) 4 mg - 12 tablet drug release (Sidmak vs. reference) in pH 6.8 Buffer

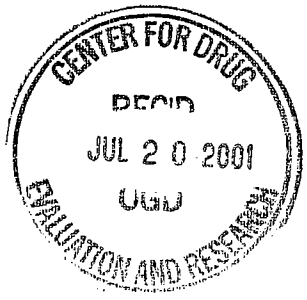
5) 8 mg - 12 tablet drug release (Sidmak vs. reference) in water
6) 8 mg - 12 tablet drug release (Sidmak vs. reference) in 0.1N HCl
7) 8 mg - 12 tablet drug release (Sidmak vs. reference) in pH 4.5 Buffer
8) 8 mg - 12 tablet drug release (Sidmak vs. reference) in pH 6.8 Buffer

Should you have any questions or require any additional information, please do not hesitate to contact either Mr. Roger Schwede at (973) 599-4352 or myself at (973) 599-4353.

Sincerely,

Deborah L. Pakay

Deborah L. Pakay
Manager, Regulatory Affairs



Sidmak LABORATORIES, INC.

17 WEST STREET ● P.O. BOX 371 ● EAST HANOVER, NJ 07936 ● TELEPHONE: (973) 386-5566 ● (800) 922-0547

ORIG AMENDMENT
N/AB

August 3, 2001

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Albuterol Sulfate Extended-release Tablets 4 mg and 8 mg
ANDA #76-130 ***BIOEQUIVALENCY AMENDMENT***

Dear Sir/Madam:

Reference is made to the agency's telephone conversation on 8/2/01 between Dr. Nina Nwaba, Dr. Singhe and myself. During this call, we were asked to include the %RSD for each of the dissolution profiles submitted previously on 7/19/01. Included in this amendment are the requested profiles, which include the %RSD's.

1) 4 mg - 12 tablet drug release (Sidmak vs. reference) in water
2) 4 mg - 12 tablet drug release (Sidmak vs. reference) in 0.1N HCl
3) 4 mg - 12 tablet drug release (Sidmak vs. reference) in pH 4.5 Buffer
4) 4 mg - 12 tablet drug release (Sidmak vs. reference) in pH 6.8 Buffer

5) 8 mg - 12 tablet drug release (Sidmak vs. reference) in water
6) 8 mg - 12 tablet drug release (Sidmak vs. reference) in 0.1N HCl
7) 8 mg - 12 tablet drug release (Sidmak vs. reference) in pH 4.5 Buffer
8) 8 mg - 12 tablet drug release (Sidmak vs. reference) in pH 6.8 Buffer

Should you have any questions or require any additional information, please do not hesitate to contact either Mr. Roger Schwede at (973) 599-4352 or myself at (973) 599-4353.

Sincerely,

Deborah L Pakay

Deborah L. Pakay
Manager, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
AUG 0 6 2001
OGD

Archival

Sidmak LABORATORIES, INC.

17 WEST STREET ● P.O. BOX 371 ● EAST HANOVER, NJ 07936 ● TELEPHONE: (973) 386-5566 ● (800) 922-0547

August 7, 2001

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP

51 C

Re: Albuterol Sulfate Extended-release Tablets 4 mg and 8 mg
ANDA #76-130 ***BIOEQUIVALENCY AMENDMENT***

Dear Sir/Madam:

Reference is made to the telephone conversation on 8/7/01 between Dr. Nina Nwaba (OGD), the reviewer (OGD) and myself. During this call, we were asked to state what type of medium was used for the pH 4.5 and pH 6.8 Buffers used in the dissolution testing for both strengths of this product.

1) 4 mg - 12 tablet drug release (Sidmak vs. reference) in pH 4.5, medium was a phosphate buffer.
2) 4 mg - 12 tablet drug release (Sidmak vs. reference) in pH 6.8, medium was a phosphate buffer.
3) 8 mg - 12 tablet drug release (Sidmak vs. reference) in pH 4.5, medium was a phosphate buffer.
4) 8 mg - 12 tablet drug release (Sidmak vs. reference) in pH 6.8, medium was a phosphate buffer.

Should you have any questions or require any additional information, please do not hesitate to contact either Mr. Roger Schwede at (973) 599-4352 or myself at (973) 599-4353.

Sincerely,

Deborah L Pakay

Deborah L. Pakay
Manager, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
AUG 0 9 2001
OGD

MINOR AMENDMENT

ANDA 76-130

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

AUG 14 2001

TO: APPLICANT: Sidmak Laboratories, Inc. TEL: 973-386-5566 ext 4352

ATTN: Roger W. Schwede FAX: 973-599-5721

FROM: Kassandra Sherrod PROJECT MANAGER: 301-827-5849

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated March 2, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Albuterol Sulfate Extended-release Tablets, 4 mg and 8 mg.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Chemistry deficiencies KS

Redacted 2 page(s)

of trade secret and/or

confidential commercial

information from

8/14/2001 FDA FAX

Sidmak LABORATORIES, INC.

17 WEST STREET ● P.O. BOX 371 ● EAST HANOVER, NJ 07936 ● TELEPHONE: (973) 386-5566 ● (800) 922-0547

November 16, 2001

N/Amy
ORIG AMENDMENT

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Albuterol Sulfate Extended-release Tablets 4 mg and 8 mg
ANDA #76-130 ***RESPONSE TO A MINOR AMENDMENT LETTER***

Dear Sir/Madam:

Reference is made to the agency's communication dated 8/14/01 (copy attached), which provided chemistry comments for the above-mentioned application. This response should be considered a Minor Amendment.

The following represents Sidmak's response to the agency's comments. For your convenience, the comment is copied as it appeared on the letter and has been italicized. Sidmak's response is printed underneath the comment for each item.

1. *DMF —— is deficient and the holder has been informed.*

We have been in contact with ———————— regarding these deficiencies. It is our understanding that ———— has responded to all deficiencies on 10/29/01. Please refer to **Attachment 1** for a copy of their cover letter.

2. [redacted] statements regarding

NOV 19 2001
EVALUATION AND RESEARCH

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of trade secret and/or

confidential commercial

information from

11/16/2001 SIDMAK LETTER

10. *Please submit available updated room temperature stability data for the product and include your current stability specifications on the stability data report form.*

Included as **Attachment 7** is the updated room temperature stability data for both the 4 mg and 8 mg strengths. The stability reports reflect the current revised stability specifications for this product.

Should you have any questions or require any additional information, please do not hesitate to contact either Ms. Deborah Pakay at (973) 599-4353 or myself at (973) 599-4352.

Sincerely,

Roger Schwede
Vice President of R&D and
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Sidmak LABORATORIES, INC.

17 WEST STREET ● P.O. BOX 371 ● EAST HANOVER, NJ 07936 ● TELEPHONE: (973) 386-5566 ● (800) 922-0547

December 14, 2001

ORIG AMENDMENT
N/AM

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Albuterol Sulfate ER Tablets 4 mg and 8 mg, ANDA #76-130
TELEPHONE AMENDMENT RESPONSE

Dear Sir/Madam:

On Monday, December 3rd, in a telephone conversation with Dr. Ijeoma Namani, the following questions were posed regarding our pending application for Albuterol Sulfate ER Tablets 4 mg and 8 mg. In response to that telephone conversation, the following information is being provided.

Following the statement of the comment, we have provided Sidmak's response.

1)

2)

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confidential commercial

information from

12/14/2001 SIDMAK LETTER

Should you have any questions regarding the information contained in this response, please do not hesitate to contact either Mr. Roger Schwede at (973) 599-4352 or myself at (973) 599-4353.

Sincerely,

Deborah L. Pakay
Manager, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Please File w/ ANDA 76-130

********** -COMM. JOURNAL- ********** DATE JAN-04-2002 ***** TIME 07:33 ********

MODE = MEMORY TRANSMISSION START=JAN-04 07:32 END=JAN-04 07:33

FILE NO.=006

STN NO.	COMM.	ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
001	OK	#	919735995721	002/002	00:00:39

A.1.1
K. Sherrod
1-4-02

-FDA CDER OGD LPS -

********** - ***** - **********

FAX COVER SHEET

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Rockville, Maryland

Date: 01-04-02

TO: Roger Schwede at Sidmak lab. ANDA 76-130

Phone: 973-386-5576 Fax: 973-599-5721

From: Angela Payne

Phone: (301) 827-5846 Fax: (301) 443-3847

Number of Pages: 2
(Including Cover Sheet)

Comments:
Labeling comments for your Albuterol ER Tablets

REVIEW OF PROFESSIONAL LABELING #1 (first generic)
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **76-130** Date of Submission: March 2, 2001
Applicant's Name: Sidmak Laboratories, Inc.
Established Name: **Albuterol Extended-release Tablets, 4 mg and 8 mg**

Labeling Deficiencies:

1. GENERAL COMMENT: Please revise all labels and labeling to read "Albuterol Extended-release Tablets " rather than Albuterol Sulfate Extended-release Tablets.
2. CONTAINER (4 mg and 8 mg) 100s and 500s
   a. Please increase the prominence of " do not chew or crush".
   b. Revise each strength and the each tablet contain statement as follows:
   "(oral) 4 mg*.
   *Each extended-release tablet contains 4.8 mg of albuterol sulfate equivalent to 4 mg albuterol tablets.
3. [redacted] See comments under GENERAL COMMENTS and CONTAINER.
4. INSERT
   a. GENERAL COMMENT – Revise [redacted] tablets" to read " Albuterol tablets, USP" throughout the insert.
   b. DESCRIPTION – revise "[redacted]" to read "structural formula".
   c. HOW SUPPLIED - You may delete reference to the Ventolin trademark information.

Please revise your labels and labeling, as instructed above, and submit 12 copies of final printed labels and labeling.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes - http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Gidmak®
LABORATORIES, INC.

17 WEST STREET ● P.O. BOX 371 ● EAST HANOVER, NJ 07936 ● TELEPHONE: (973) 386-5566 ● (800) 922-0547

January 22, 2002

NDA

ORIG AMENDMENT

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Albuterol Extended-Release Tablets 4 mg and 8 mg, ANDA #76-130
RESPONSE TO LABELING LETTER

Dear Sir/Madam:

Reference is made to the agency's communication dated 01/04/02 (copy attached) which provided labeling comments for the above-mentioned application.

We have revised our container labels and package insert to reflect the revisions noted in your letter. Included with this amendment are twelve copies of final printed labeling. To facilitate review of this submission, and in accordance with 21 CFR 314.94(a)(8)(iv), we are providing a side-by-side comparison of our proposed labeling versus our previously submitted labeling with all differences annotated and explained.

Should you have any questions regarding the information contained in this response, please do not hesitate to contact either Mr. Roger Schwede at (973) 599-4352 or myself at (973) 599-4353.

Sincerely,

Deborah L. Pakay

Deborah L. Pakay
Manager, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
JAN 24 2002

Archival

Sidmak LABORATORIES, INC.

17 WEST STREET ● P.O. BOX 371 ● EAST HANOVER, NJ 07936 ● TELEPHONE: (973) 386-5566 ● (800) 922-0547

March 5, 2002

ORIG AMENDMENT
N/Am

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Albuterol Sulfate ER Tablets 4 mg and 8 mg, ANDA #76-130
AMENDMENT TO A PENDING APPLICATION

Dear Sir/Madam:

As discussed in our telephone conversation with Ms. Kassandra Sherrod on Monday, March 4th, Sidmak Laboratories has recognized the need to make further modifications to the amendment filed on December 14th, 2001.

[redacted]

DRUG
MAR 06 2002
EVALUATION AND RESEARCH

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

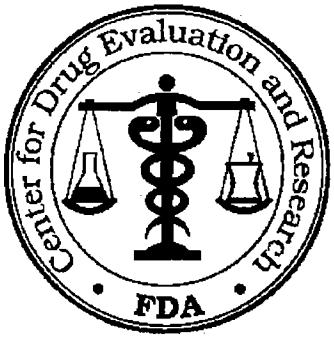
3/5/2002 SIDMAK LETTER

BIOEQUIVALENCY AMENDMENT

ANDA 76-130

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

MAY 10 2002



APPLICANT: Sidmak labs

TEL: 973-599-4352

ATTN: Roger Schwede

FAX: 973-599-5721

FROM: Nina Nwaba

PROJECT MANAGER: 301-827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on December 14, 2001, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Albuterol Sulfate Tablets, 8 mg, and 4 mg.

Reference is also made to your amendment(s) dated: March 5, 2002.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __1_ page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS: The following dissolution specification should be incorporated into you finished product release and stability specifications. Please revise and resubmit these specifications accordingly. The response should be noted as a "Telephone Amendment".

MAY 10 2002

BIOEQUIVALENCY DEFIENCY TO BE PROVIDED TO THE APPLICANT

ANDA/AADA: 76-130 APPLICANT: Sidmak Laboratories

DRUG PRODUCTS: Albuterol sulfate extended release tablets, 4 & 8 mg

The Division of Bioequivalence has completed its review and it has identified the following deficiencies.

You were previously provided with the following dissolution specifications.

Time (Hr)	% Dissolution
2	———
4	———
6	———
8	NLT ——

The Agency's specifications were the same for both the 4-mg and 8-mg tablets. You are requesting separate dissolution specifications for these products. Furthermore your proposed specifications are different based on the December 14, 2001 March 5, 2002 amendments. Please provide justification for different dissolution specifications for the 4-mg and 8-mg product.

It is also noted that the Agency's specifications included % dissolution determination at 2, 4, 6 and 8 hours, whereas the your proposal is based dissolution at 4, 6 and 10 hours.

Based on the March 5, 2002 amendment, dissolution time points for the ANDA stability study and QC release are 1, 2, 4, 6, 8 and hours, and 2, 6, and 10 hours respectively. Time points selected for dissolution testing should be the same for ANDA related studies and QC release. You are requested to use the time points mentioned in the specifications outlined above.

You were informed that the above dissolution specifications were provided on an interim basis, final recommendation would be made upon review of dissolution data for three commercial lots. You have not submitted the requested three-lot data. In the absence of the data, the Agency cannot revise its recommendation for the interim dissolution specifications.

Sincerely yours,

for Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Sidmak LABORATORIES, INC.

17 WEST STREET ● P.O. BOX 371 ● EAST HANOVER, NJ 07936 ● TELEPHONE: (973) 386-5566 ● (800) 922-0547

May 21, 2002

N/AB

ORIG AMENDMENT

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Albuterol Sulfate ER Tablets 4 mg and 8 mg, ANDA #76-130
RESPONSE TO BIOEQUIVALENCY AMENDMENT

Dear Sir/Madam:

This letter is in response to the deficiency letter received by Sidmak Lab's dated May 10th, 2002 (copy attached) and also more specifically in response to the telephone conversation held between Mr. Roger Schwede and Dr. Nina Nwaba from the Division of Bioequivalence on Friday May 17th.

The May 10th letter referred to dissolution specifications that the division had thought were communicated to us several months earlier, but in fact never were included in chemistry comments. Had they, the basis of our amendment of 12/14/01 would have addressed the issue and these current communications could have been precluded.

The critical issue remains the establishment of dissolution specifications. We acknowledge the Divisions comment that the specifications may be considered tentative until we have manufactured three commercial batches, however the specifications proposed by the division are at issue. From our data neither the ANDA batch nor the reference product, Volmax®, meet the criteria. The data contained in **Attachment 1** plot the results for the two biobatches and the two reference products on a graph with FDA's proposed specifications.

The letter of May 10th further questioned the proposal to have separate specifications for both strengths. Sidmak conducted separate studies on each strength, consistent with bioequivalency study criteria in place when initial studies were undertaken. Because it was our observation that the two strengths of the reference product exhibited different profiles, different specifications were justified.

Further, as we do utilize a completely different sustained release mechanism, it is not unrealistic that the in-vitro results will not fully compare between the test/reference products. Lastly, we note that your communication does not specify the medium to be used for the dissolution testing. We have previously responded to questions regarding in-vitro performance in multi-media. This data can be found in our bioequivalency amendment submitted on 08/03/01.

We are now at the point where we have planned for the processing of validation batches in anticipation of a product launch as all other chemistry deficiencies and labeling have been addressed. The proposed Sidmak specifications and those from the Division of Bioequivalence are again shown here.

	Sidmak's Proposed		Div. of Bioequivalence
	4 mg	8 mg	4 mg and 8 mg
2nd Hour	NMT — %	NMT — %	2nd Hour ___
6th Hour	___ %	___ %	4th Hour ___
10th Hour	NLT — %	NLT —	6th Hour ___
			8th Hour NLT ___

At this time, we are requesting a conference call to discuss and resolve these issues. Should you have any questions regarding the information contained in this response, please do not hesitate to contact either Ms. Debbie Pakay at (973) 599-4353 or myself at (973) 599-4352.

Sincerely,

Deborah Pakay

for Roger Schwede
Vice President of R&D and Regulatory Affairs

MINOR AMENDMENT

ANDA 76-130

MAY 23 2002

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Sidmak Laboratories, Inc. TEL: 973-599-4352

ATTN: Roger Schwede FAX: 973-599-5721

FROM: Nicole Park PROJECT MANAGER: 301-827-5849

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated March 2, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Albuterol Sulfate Extended-Release Tablets, 4 mg and 8 mg.

Reference is also made to your amendment(s) dated: November 16, and December 14, 2001; January 22 and March 5, 2002.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__1__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

NP

MAY 23 2002

38. Chemistry comments to be provided to the applicant

ANDA: **76-130** APPLICANT: Sidmak Laboratories, Inc.

DRUG PRODUCT: Albuterol Sulfate Extended Release Tablets, 4 mg and 8 mg

The following deficiencies represent MINOR deficiencies:

The Division of Bioequivalence has requested additional information regarding your dissolution testing methodology, release and stability specifications, and time points. We await a response to the deficiency letter sent by the Bioequivalence Division on May 10th, 2002.

Sincerely yours,

for

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Sidmak LABORATORIES, INC.

17 WEST STREET ● P.O. BOX 371 ● EAST HANOVER, NJ 07936 ● TELEPHONE: (973) 386-5566 ● (800) 922-0547

May 31, 2002

N/Am

ORIG AMENDMENT

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Albuterol Sulfate ER Tablets 4 mg and 8 mg, ANDA #76-130
MINOR AMENDMENT RESPONSE

Dear Sir/Madam:

Reference is made to the agency's communication faxed to Sidmak on 5/23/02 (copy attached) which noted that we needed to respond to the Div. of Bioequivalence letter dated 5/10/02.

This letter will confirm that Sidmak responded to the Division of Bioequivalence, by telephone on 5/17/02 (telephone conversation held between Mr. Roger Schwede and Dr. Nina Nwaba) and in writing on 5/21/02. We are currently awaiting any comments the division may have.

Should you have any questions, please do not hesitate to contact either Mr. Roger Schwede at (973) 599-4352 or myself at (973) 599-4353.

Sincerely,

Deborah L. Pakay
Manager, Regulatory Affairs

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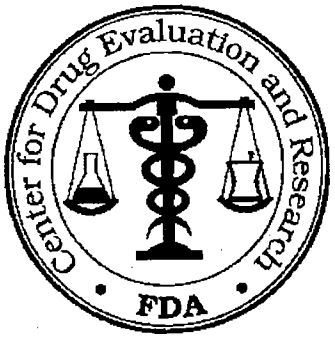
6/1/02

BIOEQUIVALENCY AMENDMENT

ANDA 76-130

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

JUN 20 [redacted]



APPLICANT: Sidmak Laboratories, Inc.

TEL: 973-599-4352

ATTN: Roger Schwede

FAX: 973-599-5721

FROM: Nina Nwaba

PROJECT MANAGER: 301-827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on May 21, 2002, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Albuterol Sulfate Extended Release Tablets, 4 mg and 8 mg.

Reference is also made to you amendment dated May 31, 2002.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __1_ page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS: The following dissolution specification should be incorporated into you finished product release and stability specifications. Please revise and resubmit these specifications accordingly. The response should be noted as a "Telephone Amendment".

BIOEQUIVALENCY DEFIENCY TO BE PROVIDED TO THE APPLICANT

ANDA/AADA: 76-130

APPLICANT: Sidmak Laboratories

DRUG PRODUCTS: Albuterol sulfate extended release tablets, 4 & 8 mg

The Division of Bioequivalence has completed its review and it has identified the following deficiencies.

Your proposal for separate dissolution specifications for the 4-mg and 8-mg tablets is not acceptable, because (1) these two products have similar formulations and (2) based on the data submitted previously, both products meet the Agency's specification when dissolution was conducted in water. Based on those data, you were provided with the following dissolution specifications.

Time (Hr)	% Dissolution
2	———
4	———
6	———
8	NLT —

Dissolution data submitted in the current amendment (May 21, 2002) are different from those submitted on July 19 and August 3,2001, based on which the Agency recommended the interim specifications.

Based on the July 19 and August 3 amendments, the Agency recommended dissolution testing in de-ionized water, not in ———. If you wish to submit additional dissolution data, it should be based on the recommended method (900 mL of de-ionized water, apparatus II (paddle at 50 rpm).

You have been informed that the above dissolution specifications were provided on an interim basis, final recommendation would be made upon review of dissolution data for three commercial lots. You have not submitted the requested three-lot data. In the absence of the data, the Agency cannot revise its recommendation for the interim dissolution specifications.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Sidmak® LABORATORIES, INC.

17 WEST STREET ● P.O. BOX 371 ● EAST HANOVER, NJ 07936 ● TELEPHONE: (973) 386-5566 ● (800) 922-0547

June 21, 2002

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/A B

Re: Albuterol Sulfate ER Tablets 4 mg and 8 mg
ANDA #76-130
RESPONSE TO BIOEQUIVALENCY AMENDMENT

Dear Sir/Madam:

This letter is in response to the deficiency letter received by Sidmak Laboratories dated June 20, 2002 (copy attached) from the Division of Bioequivalence. This response should be considered a bioequivalency amendment.

There seems to have been some confusion on both our parts regarding the dissolution method and specifications for this product. As the interim specifications are based on data previously submitted by Sidmak (amendments dated July 19 and August 3, 2001) we have adopted these specifications for our product. As requested in your letter, we have revised our finished product release and stability dissolution specifications/methods to reflect 900 mL of de-ionized water, apparatus II (paddle) at 50 rpm. The interim specifications for both strengths of this product will be:

2^{nd} Hour —
4^{th} Hour —
6^{th} Hour —
8^{th} Hour NLT –%

We understand that these are interim specifications and that final specifications will be recommended by the division upon review of the dissolution data from three commercial lots.

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Should you have any questions regarding the information contained in this response, please do not hesitate to contact either Ms. Debbie Pakay at (973) 599-4353 or myself at (973) 599-4352.

Sincerely,

Deborah L. Pakay

Deborah L. Pakay
Manager, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Sidmak LABORATORIES, INC.

17 WEST STREET ● P.O. BOX 371 ● EAST HANOVER, NJ 07936 ● TELEPHONE: (973) 386-5566 ● (800) 922-0547

September 23, 2002

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AM

Re: Albuterol Sulfate ER Tablets 4 mg and 8 mg
ANDA #76-130, ***TELEPHONE AMENDMENT***

Dear Sir/Madam:

This communication is in response to the telephone conversation between Dr. Frank Holcombe, Office of Generic Drugs and Mr. Roger Schwede, Sidmak Laboratories and myself on Friday, September 20, 2002. This response should be considered a telephone amendment.

During this conversation, Dr. Holcombe requested that we perform additional dissolution profiles on samples retained from our accelerated stability studies and our current long-term stability studies. The profiles were to be performed in water and ———. At the same time, Sidmak offered to include profiles on the first validation batch, for each strength.

Included with this submission are the following:

1) Originally submitted profile for the 4 mg strength (lot #00-039T) performed in ———

2) Profile run on 4 mg strength (lot #00-039T) accelerated retained sample
3 months 40°C & 75%RH + 19 months & 20 days at ambient temperature

3) Profile run on 4 mg strength (lot #00-039T) long-term retained samples
18 months 25°C &60% RH + 4 months & 24 days at ambient temperature

4) Profile run on 4 mg strength (lot #7542001) first validation batch

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5) Originally submitted profile for the 8 mg strength (lot #00-016T) performed in [redacted]

6) Profile run on 8 mg strength (lot #00-016T) long-term retained samples 18 months 25°C &60% RH + 4 months & 17 days at ambient temperature

7) Profile run on 8 mg strength (lot #7582001) first validation batch

Unfortunately, the accelerated samples for the 8 mg strength (lot #00-016T) were not retained, therefore we have no samples for the additional testing.

All profiles were performed utilizing 900 mL of de-ionized water, apparatus II (paddle) at 50 rpm. A comparison of the test results indicates that the profiles are similar for the [redacted] media.

Should you have any questions regarding the information contained in this response, please do not hesitate to contact either Mr. Roger Schwede at (973) 599-4352 or myself at (973) 599-4353.

Sincerely,

Deborah L. Pakay
Manager, Regulatory Affairs