CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-343

Approval Letter

ANDA 75-343

NOV 9 1999

Zenith Goldline Pharmaceuticals, Inc.
Attention: Jason A. Gross
U.S. Agent for: Steripak Limited
140 Legrand Avenue
Northvale, NJ 07647-2485

Dear Sir:

This is in reference to your abbreviated new drug application dated February 27, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Albuterol Sulfate Inhalation Solution, 0.083% (base), packaged in 3 mL unit-dose vials.

Reference is also made to your amendments dated April 13, and October 8, 1999.

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 Sulfate Inhalation Solution, 0.083% (base), to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Proventil® Inhalation Solution, 0.083% (base), of Schering Corp).

Under 21 CFR 314.70, 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,

/S/

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

11/9/99

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-343

FINAL PRINTED LABELING

Albuterol Sulfate Inhalation Solution

0.083%* (2.5 mg/3 mL*)

Rx Only

Equivalent to 0.5 mL Albuterol Sulfate 0.5%* diluted to 3 mL with normal saline

* Potency expressed as Albuterol

FOR ORAL INHALATION USE ONLY

Each mL, for oral inhalation, contains albuterol sulfate equivalent to 0.83 mg albuterol in a sterile aqueous solution containing sodium chloride, and hydrochloric acid to adjust pH.

Attention Pharmacist Detach "Patient's Instructions for Use" from package insert and dispense with solution. See package insert for Dosage and Administration.

Store between 2°C and 25°C (36°F and 77°F). Protect from light.

Retain in carton until time of use.

5 x 3-mL Sterile Unit Dose Vials

Manufactured for:

Zenith Goldline Pharmaceuticals Inc., MIAMI, FL 33137

By: Steripak Ltd., Runcorn, Cheshire WA7 1QF England

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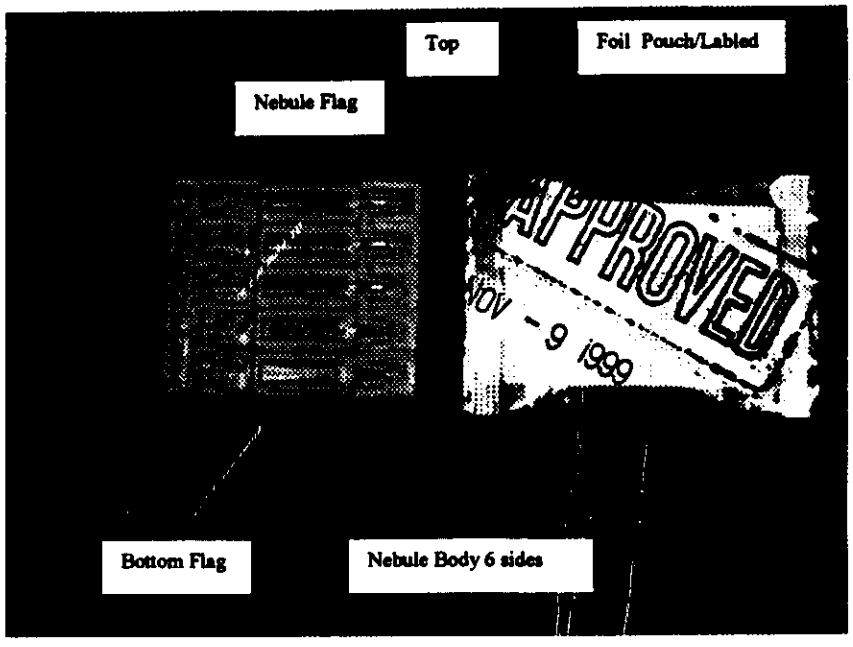
070 d

Non-Embossed Nebule (set of 5) and
Nebules in Foil Pouch



Proposed Embossing Text of Nebule:

Bottom Flag: (There are two sides)
Side one front: Albuterol Sulfate Inhalation Solution
Side two back: Zenith Goldline Pharmaceuticals

Nebule Flag: (There are two sides)
Side one front: Lot Number and Expiration Date
Side two back: Individual Nebule number Not for Injection

Nebule Body: (There are six sides)
Front three sides.
Top side: Zenith Goldline
Middle side: Albuterol Sulfate Inhalation Solution
Bottom side: 0.083%* (2.5 mg/3 mL*)
Back three sides:
Top Side: No Text (Blank)
Middle side: For Oral Inhalation Use Only
Bottom: Sterile

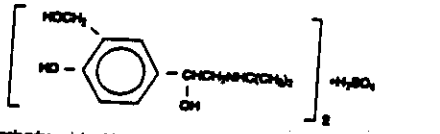
Top : (There are two sides)
Side one: No Text (Blank)
Side two: No Text (Blank)

46 01111

ALBUTEROL SULFATE
INHALATION SOLUTION 0.083%*
("Potency expressed as albuterol)
PRESCRIBING INFORMATION
Rx Only

APPROVED

DESCRIPTION: Albuterol sulfate inhalation solution is a relatively selective beta$_2$-adrenergic bronchodilator (see CLINICAL PHARMACOLOGY section below). Albuterol sulfate, the racemic form of albuterol, has the chemical name α^1-[(tert-butylamino)-methyl]-4-hydroxy-m-xylene-α,α'-diol sulfate (2:1)(salt), and the following chemical structure:



Albuterol sulfate has a molecular weight of 576.71 and the molecular formula $(C_{13}H_{21}NO_3)_2H_2SO_4$. 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.

Albuterol sulfate inhalation solution 0.083%* requires no dilution before administration.

Each mL of albuterol sulfate inhalation solution (0.083%) contains 0.83 mg of albuterol (as 1 mg of albuterol sulfate) in an isotonic, sterile, aqueous solution containing sodium chloride, and hydrochloric acid to adjust the pH between 3 and 5. Albuterol sulfate inhalation solution (0.083%) contains no sulfiting agents.

Albuterol sulfate inhalation solution is a clear, colorless to light yellow solution.

CLINICAL PHARMACOLOGY: The primary action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (cyclic AMP) from adenosine triphosphate (ATP). The cyclic AMP thus formed mediates the cellular responses. 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.

In vitro studies and in vivo pharmacologic studies have demonstrated that albuterol has a preferential effect on beta$_2$-adrenergic receptors compared with isoproterenol. While it is recognized that beta$_2$-adrenergic receptors are the predominant receptors in bronchial smooth muscle, data indicate that there is a population of beta$_2$-receptors in the human heart existing in a concentration between 10% and 50%. The precise function of these receptors has not been established.

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

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.

The effects of rising doses of albuterol and isoproterenol aerosols were studied in volunteers and asthmatic patients. Results in normal volunteers indicated that the propensity for increase in heart rate for albuterol is 1/2 to 1/4 that of isoproterenol. In asthmatic patients similar cardiovascular differentiation between the two drugs was also seen.

Preclinical: Intravenous studies in rats with albuterol sulfate have demonstrated that albuterol crosses the blood-brain-barrier and reaches brain concentrations that are amounting to approximately 5% 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 (marmoset, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

Pharmacokinetics: After either IPPB or nebulizer administration in asthmatic patients, less than 20% of a single albuterol dose was absorbed; the remaining amount was recovered from the nebulizer and apparatus and expired air. Most of the absorbed dose was recovered in the urine 24 hours after drug administration. Following a 3 mg dose of nebulized albuterol, the maximum albuterol plasma level at 0.5 hour was 2.1 ng/ml. (range 1.4 to 3.2 ng/mL). It has been demonstrated that the following oral administration of 4 mg of albuterol, the elimination half-life was 5 to 6 hours.

Clinical Trials: In controlled clinical trials, most patients exhibited an onset of improvement in pulmonary function within 5 minutes as determined by FEV_1. FEV_1 measurements also showed that the maximum average improvement in pulmonary function usually occurred at approximately 1 hour following inhalation of 2.5 mg of albuterol by compressor-nebulizer, and remained close to peak for 2 hours. Clinically significant improvement in pulmonary function (defined as maintenance of a 15% or more increase in FEV_1 over baseline values) continued for 3 to 4 hours in most patients and in some patients continued up to 6 hours.

INDICATIONS AND USAGE: Albuterol sulfate inhalation solution is indicated for the relief of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease and acute attacks of bronchospasm.

CONTRAINDICATIONS: Albuterol sulfate inhalation solution is contraindicated in patients with a history of hypersensitivity to albuterol or any of its components.

WARNINGS:

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 sulfate inhalation solution 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 agents, 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 sulfate inhalation solution can produce paradoxical bronchospasm, which may be life-threatening. If paradoxical bronchospasm occurs, albuterol sulfate inhalation solution should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new vial.

Cardiovascular Effects: Albuterol sulfate inhalation solution, 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 sulfate inhalation solution 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 QT$_c$ interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, albuterol sulfate inhalation solution, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias and hypertension.

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

Microbial Contamination: To avoid microbial contamination, the entire contents of the unit-dose vial should be administered immediately after the vial has been opened for the first time.

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.

Large doses of intravenous albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. As with other beta-agonist medications, 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 potassium supplementation.

Information for Patients: See Illustrated PATIENT'S INSTRUCTIONS FOR USE.

General: The action of albuterol sulfate inhalation solution may last up to 6 hours or longer. Albuterol sulfate inhalation solution should not be used more frequently than recommended. Do not increase the dose or frequency of doses of albuterol sulfate inhalation solution without consulting your physician. If you find that treatment with albuterol sulfate inhalation solution 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 sulfate inhalation solution, 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 the use of albuterol sulfate inhalation solution.
Effective use of albuterol sulfate inhalation solution includes understanding of the way that it should be administered. See Illustrated "PATIENT'S INSTRUCTIONS FOR USE".

Microbial Contamination: To avoid microbial contamination, the entire contents of the unit-dose vial should be administered immediately after the vial has been opened for the first time.

Mixing Different Inhalation Solutions: Drug compatibility (physical and chemical), efficacy, and safety of albuterol sulfate inhalation solution when mixed with other drugs in a nebulizer have not been established.

Drug Interactions: Other short-acting sympathomimetic aerosol bronchodilators or epinephrine should not be used concomitantly with albuterol.

Beta Blockers: Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta-agonists, such as albuterol sulfate inhalation solution, 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.

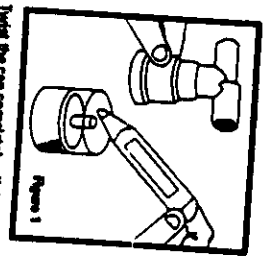
PHARMACIST – DETACH HERE AND GIVE LOWER PORTION TO PATIENT

Patient's Instructions for Use
ALBUTEROL SULFATE
Inhalation Solution 0.083%*
("Potency expressed as albuterol)

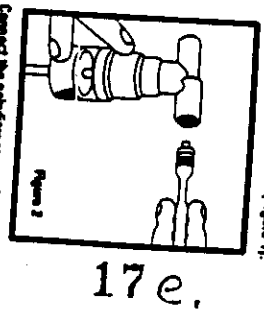
Note: This is a unit-dose vial. No dilution is required.

Read complete instructions carefully before using.

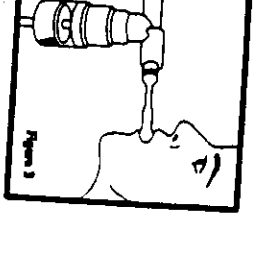
1. Twist the cap completely off the vial and squeeze the entire contents into the nebulizer reservoir (Figure 1).



2. Connect the nebulizer reservoir to the mouthpiece or face mask (Figure 2).
3. Connect the nebulizer to the compressor.



4. Sit in a comfortable, upright position; place the mouthpiece in your mouth (Figure 3) or put on the face mask; and turn on the compressor.
5. Breathe as calmly, deeply and evenly as possible until no more mist is formed in the nebulizer chamber (about 5–15 minutes). At this point, the treatment is finished.



Instructions continued overleaf

17e.

Electrolyte: 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 co-administration 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 this finding 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.

Monoamine Oxidase Inhibitors or Tricyclic Antidepressants: Albuterol should be administered with extreme caution in 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.

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 mesenterium at oral dose dietary doses of 2 mg/kg (approximately 2 times the maximum recommended daily inhalation dose for adults 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 up to 500 mg/kg (approximately 200 times the maximum recommended daily inhalation dose for adults on a mg/m² basis). In a 22 month study in the Golden Hamster, albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 50 mg/kg (approximately 25 times the maximum recommended daily inhalation dose for adults on a mg/m² basis).

Albuterol sulfate was not mutagenic in the Ames test with or without metabolic activation using tester strains *S. typhimurium* TA1537, TA1535, and TA98 or *E. coli* WP2, WP2uvrA, and WP67. No forward mutation was seen in yeast strain *S. cerevisiae* S9 nor any meiotic gene conversion in yeast strain *S.cerevisiae* JD1 with or without metabolic activation. Pneumotox 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.

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses of albuterol sulfate up to 50 mg/kg (approximately 40 times the maximum recommended daily inhalation 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 sub-cutaneous (sc) doses at and above 0.25 mg/kg, corresponding to less than the maximum recommended daily inhalation dose for adults on a mg/m² basis, induced cleft palate formation in 6 of 111 (4.9%) fetuses. At a subcutaneous dose of 2.5 mg/kg, (approximately equal to the maximum recommended daily inhalation dose for adults on a mg/m² basis) albuterol sulfate induced cleft palate formation in 19 of 108 (18.3%) fetuses. The drug did not induce cleft palate formation when administered at a subcutaneous dose of 0.025 mg/kg (corresponding to less than the maximum recommended daily inhalation dose for adults on a mg/m² basis). Cleft palate also occurred in 22 of 72 (30.9%) fetuses from females treated with 2.5 mg/kg isoproterenol (positive control) administered subcutaneously.

A reproduction study in Swiss Dutch rabbits revealed exencephalia in 7 of 19 (37%) fetuses when albuterol was administered orally at a dose of 50 mg/kg (approximately 80 times the maximum recommended daily inhalation dose for adults on a mg/m² basis).

Studies in pregnant rats with tritiated albuterol demonstrated that approximately 10% of the circulating maternal drug is transferred to the fetus. Deposition in the fetal lungs is comparable to maternal lungs, but fetal liver deposition is 1% of the maternal liver levels.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, 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 reported in the offspring of patients being treated with albuterol. Some of the mothers were taking multiple medications during their pregnancies. Because no consistent pattern of defects can be discerned, a relationship between albuterol use and congenital anomalies has not been established.

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

Toxolysis: Albuterol has not been approved for the management of preterm labor. The benefit : risk ratio when albuterol is administered for toxolysis has not been established. Serious adverse reactions, including maternal pulmonary edema, have been reported during or following treatment of premature labor with beta-agonists, including albuterol.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because of the potential for tumorigenicity shown for albuterol in some 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: Safety and effectiveness of albuterol sulfate in pediatric patients below the age of 12 years have not been established.

ADVERSE REACTIONS: The results of clinical trials with albuterol sulfate inhalation solution in 136 patients showed the following side effects which were considered probably or possibly drug related:

PERCENT INCIDENCE OF ADVERSE REACTIONS

REACTION	PERCENT INCIDENCE
Central Nervous System	
Tremors	20%
Dizziness	7%
Nervousness	4%
Headache	3%
Insomnia	1%
Gastrointestinal	
Nausea	6%
Dyspepsia	1%
Ear, Nose and Throat	
Nasal Congestion	1%
Pharyngitis	<1%
Cardiovascular	
Tachycardia	1%
Hypertension	1%
Respiratory	
Bronchospasm	8%
Cough	4%
Bronchitis	4%
Wheezing	1%

No clinically relevant laboratory abnormalities related to albuterol sulfate inhalation solution were determined in these studies.

Cases of urticaria, rash, bronchospasm, hoarseness, oropharyngeal edema and anhydrosis (including atrial fibrillation, supraventricular tachycardia, extrasystoles) have also been reported after the use of inhaled albuterol.

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., angina, hypertension, tachycardia with rates up to 200 beats per minute, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, malaise, and insomnia. In addition, seizures, hypotension, fatigue, and hypokalemia may also occur. As with all sympathomimetic aerosol medications, cardiac arrest and even death may be associated with abuse of albuterol sulfate inhalation solution.
Treatment consists of discontinuation of albuterol sulfate inhalation solution 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 sulfate inhalation solution. The oral median lethal dose of albuterol sulfate in mice is greater than 3000 mg/kg (approximately 810 times the maximum recommended daily inhalation dose for adults on a mg/m² basis). In mature rats, the subcutaneous (sc) median lethal dose of albuterol sulfate is approximately 450 mg/kg (approximately 360 times the maximum recommended daily inhalation dose for adults on a mg/m² basis). In small young rats, the subcutaneous median lethal dose is approximately 2000 mg/kg (approximately 1600 times the maximum recommended daily inhalation dose for adults on a mg/m² basis). The inhalational median lethal dose has not been determined in animals.

DOSAGE AND ADMINISTRATION
The usual dosage for adults and pediatric patients 12 years of age and older is 2.5 mg of albuterol administered 3 to 4 times daily by nebulization. More frequent administration or higher doses are not recommended. To administer 2.5 mg of albuterol, administer the entire contents of one unit-dose vial (3 mL of 0.083% inhalation solution) by nebulization. The flow rate is regulated to suit the particular nebulizer so that the albuterol sulfate inhalation solution will be delivered over approximately 5 to 15 minutes.

Drug compatibility (physical and chemical), efficacy, and safety of albuterol sulfate inhalation solution when mixed with other drugs in a nebulizer have not been established.

The use of albuterol sulfate inhalation solution can be continued as medically indicated to control recurring bouts of bronchospasm. During treatment, most patients gain optimum benefit from regular use of the nebulizer solution.

If a previously effective dosage regimen fails to provide the usual relief, medical advice should be sought immediately, as this is often a sign of seriously worsening asthma which would require reassessment of therapy.

Microbial Contamination: To avoid microbial contamination, the entire contents of the unit-dose vial should be administered immediately after the vial has been opened for the first time.

The nebulizer should be cleaned in accordance with the manufacturer's instructions. Failure to do so could lead to bacterial contamination of the nebulizer, and possible infection.

HOW SUPPLIED: Albuterol sulfate inhalation solution 0.083% is a clear, colorless to light yellow solution, and is supplied in unit dose vials of 3 mL each.

Unit Dose boxes of 25 each - NDC 0172-6405-44

Unit Dose boxes of 60 each (2 x 30) - NDC 0172-6405-48

Store between 2°C and 25°C (36°F and 77°F). Protect from light. Retain in carton until time of use.

Manufactured for: Zenith Goldline Pharmaceuticals, Inc., Miami, FL 33137
by: Steripak Limited, Runcorn, Cheshire WA7 1QF England

PHARMACIST – DETACH HERE AND GIVE LOWER PORTION TO PATIENT

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6. Clean the nebulizer (see manufacturer's instructions). Failure to clean the nebulizer in accordance with the manufacturer's instructions could lead to bacterial contamination of the nebulizer, and possible infection.

Note: Use only as directed by your physician. More frequent administration or higher doses are not recommended.

Mixing Compatibility: The safety and effectiveness of albuterol sulfate inhalation solution have not been determined when one or more drugs are mixed with it in a nebulizer. Check with your physician before mixing any medications in your nebulizer.

Microbial Contamination: To avoid microbial contamination, the entire contents of the unit-dose vial should be administered immediately after the vial has been opened for the first time.

Store Albuterol Sulfate Inhalation Solution 0.083%* between 2°C and 25°C (36°F and 77°F).

Protect from light. Retain in carton until time of use.

ADDITIONAL INSTRUCTIONS:

Job no	1461
Date	16/04/99
Designer	MC
Draft	04
Revision	MC 29/04/99
Product	Albuterol Sulfate
Component	Carton
Strength	3ml (x30)
Livery	ZG
Territory	US
Dimensions	L 95 x W 90 x D 125mm
Bar code	—
Specification Reference	—
Other information	
Pharma code	—
Software	Illustrator 7

Norton Healthcare
Design Department

Colours
Profile (Not for print)
PMS Reflex Blue
PMS Magenta
PMS 873

Colour Tint
30% & 50% Magenta

Fonts
Zurich BT
Swiss 721 RT
Symbol (job box)

Norton Healthcare Ltd
Supplier Instructions

Artwork text and content must not be reset, remade, amended or altered. The only exceptions to this are:

- to items where you are requested to add an EAN bar code
- to printed cartons, where print stations, security codes for printing purposes and your logo may be added in positions that are not visible on the assembled carton.
- bleeds, chokes, spreads or other adjustments required for print production purposes only.

If you have any difficulties please contact the Norton Healthcare Ltd Artwork Co-ordinator or Assistant

Electronic artwork or Colour separated bromide artwork need not be returned.

If it is retained, you are responsible for ensuring that it is securely stored.

Transparencies and or mounted artwork must be returned, adequately packed to Norton Healthcare's Design Department.

CDs, Zip disks and floppy disks etc must be returned.

Draft approved for Circulation Signature Date / /	Packaging Technology approval Signature Date / /	Regulatory Affairs approval Signature Date / /

PC 0780

Zenith Goldline

ALBUTEROL SULFATE

INHALATION SOLUTION

0.083%*
2.5 mg/3 mL*

Equivalent to 0.5 mL Albuterol Sulfate .5%* diluted to 3 mL with normal saline

* POTENCY EXPRESSED AS ALBUTEROL

Rx Only

STERILE UNIT DOSE VIALS
FOR ORAL INHALATION USE ONLY
NOT FOR INJECTION
PREDILUTED WITH NORMAL SALINE

30 x 3 mL UNIT DOSE VIALS

PLACE YOUR PRESCRIPTION LA

SPECIAL PACKAGE N

UPC Placement

2

30 x 3 mL UNIT DOSE VIALS

STERILE UNIT DOSE VIALS • FOR ORAL INHALATION USE ONLY
NOT FOR INJECTION • PREDILUTED WITH NORMAL SALINE

Coding Area
Keyline does
not print

0.083%*
2.5 mg/3 mL*
* POTENCY EXPRESSED AS ALBUTEROL

ALBUTEROL SULFATE
INHALATION SOLUTION

Zenith Goldline

PLACE YOUR PRESCRIPTION LABEL HERE

USUAL DOSAGE: Read accompanying insert.
Use only as directed by your physician.
Do not exceed recommended dosage.

PHARMACIST: Detach "Patient's Instructions For Use" from package insert and dispense with solution.

Each mL, for oral inhalation, contains albuterol sulfate equivalent to 0.83 mg albuterol in a sterile aqueous solution containing sodium chloride. Adjusted to between pH 3 and 5 with hydrochloric acid.

Protect from Light
Retain in carton until time of use

Store between 2°C and 25°C (36°F and 77°F)

APPROVED
NOV - 9 199

UPC Placement

Manufactured for
ZENITH GOLDLINE PHARMACEUTICALS, INC.
MIAMI, FL 33137
by: Stenpak Limited
Runcorn, Cheshire WA7 1QF England

0499J

Job no	1460	Norton Healthcare Design Department	Colours: Profile (Not for print), PMS Reflex Blue, PMS Magenta, PMS 873
Date	16/04/99		
Designer	MC	Draft 04	
Revision	MC 29/04/99		
Product	Albuterol Sulfate		Colour Tint: 30% & 50% Magenta
Component	Carton	Strength: 3ml (x25)	
Livery	ZG	Territory: US	
Dimensions	L 95 x W 82 x D 125mm	Bar code —	
Specification Reference	—	Other information	Pharma code —
		Software: Illustrator 7	Fonts: Zurich BT, Swiss 721 BT, Symbol (joo box)

Norton Healthcare Ltd Supplier Instructions

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- to printed cartons, where print stations, security codes for printing purposes and your logo may be added in positions that are not visible on the assembled carton.
- bleeds, chokes, spreads or other adjustments required for print production purposes only.

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Draft approved for Circulation	Packaging Technology approval	Regulatory Affairs approval
Signature Date / /	Signature Date / /	Signature Date / /

PC 0782

Zenith Goldline

NDC 0172-6485-44

ALBUTEROL SULFATE
INHALATION SOLUTION

0.083%*
2.5 mg/3 mL*

Equivalent to 0.5 mL Albuterol Sulfate 5%* diluted to 3 mL with normal saline

* POTENCY EXPRESSED AS ALBUTEROL

Rx Only

STERILE UNIT DOSE VIALS
FOR ORAL INHALATION USE ONLY
NOT FOR INJECTION
PREDILUTED WITH NORMAL SALINE

25 x 3 mL UNIT DOSE VIALS

PLACE YOUR PRESCRIPTION LABEL HERE

UPC Placement

2

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Date
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Coding Area
Keyline does
not print

25 x 3 mL UNIT DOSE VIALS

STERILE UNIT DOSE VIALS • FOR OF AL INHALATION USE ONLY
NOT FOR INJECTION • PREDILUTED WITH NORMAL SALINE

0.083%*
2.5 mg/3 mL*
*POTENCY EXPRESSED AS ALBUTEROL

ALBUTEROL SULFATE
INHALATION SOLUTION

NDC 0172-6406-44

Zenith Goldline

APPROVED
NOV - 9 1999

USUAL DOSAGE: Read accompanying insert.
Use only as directed by your physician.
Do not exceed recommended dosage.

PHARMACIST: Detach "Patient's Instructions For Use" from package insert and dispense with solution.

Each mL, for oral inhalation, contains albuterol sulfate equivalent to 0.83 mg albuterol in a sterile aqueous solution containing sodium chloride. Adjusted to between pH 3 and 5 with hydrochloric acid.

Protect from Light
Retain in carton until time of use

Store between 2°C and 25°C (36°F and 77°F)

PLACE YOUR PRESCRIPTION LABEL HERE

UPC Placement

Manufactured for
ZENITH GOLDLINE PHARMACEUTICALS, INC.
MIAMI, FL 33137
by: Stenpak Limited
Runcorn, Cheshire WA7 1QF England

0499J

Job no	1462
Date	16/04/99
Designer	MC
Draft	02
Revision	MC 29/04/99
Product	Albuterol Sulfate
Component	Carton
Strength	
Livery	ZG
Territory	
Dimensions	L196x W92 x D130 mm
Bar	
Specification Reference	—
Other information	Updated from Medica a/w Prof: Medica A/007/189/00
Pha	
Soft	Illus

Draft approved for Circulation
Signature Date / /

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STERILE UNIT DOS
NOT FOR INJEC

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0499 J

UPC Placement

APPROVED
NOV - 9

2

STERILE UNIT DOSE VIALS • FOR ORAL INHALATION USE ONLY
NOT FOR INJECTION • PREDILUTED WITH NORMAL SALINE

* POTENCY EXPRESSED AS ALBUTEROL

0.083%*
2.5 mg/3 mL*

ALBUTEROL SULFATE
INHALATION SOLUTION

NDC 0172-6405-49

Zenith Goldline

USUAL DOSAGE: Read accompanying insert.
Use only as directed by your physician.
Do not exceed recommended dosage.

PHARMACIST: Detach "Patient's Instructions For Use" from package insert and dispense with solution.

Each mL, for oral inhalation, contains albuterol sulfate equivalent to 0.83 mg albuterol in a sterile aqueous solution containing sodium chloride. Adjusted to between pH 3 and 5 with hydrochloric acid.

Protect from Light
Retain in carton until time of use

Store between 2°C and 25°C (36°F and 77°F)

Manufactured for:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
MIAMI, FL 33137
by: Stenpak Limited
Runcorn, Cheshire WA7 1QF England

0499 J

UPC Pl

073

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-343

CHEMISTRY REVIEW(S)

Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **CHEMIST'S REVIEW NO.**: No. 5

2. **ANDA #** 75-343

3. **NAME AND ADDRESS OF APPLICANT:**
Steripak Limited
Goddard Road, Astmoor, Runcorn
Chesire, WA7 1QF, England

U.S. Agent:
Zenith Goldline Pharmaceuticals
U.S. Agent for Steripak Limited
Attention: Jason A. Gross
140 Legand Avenue
Northvale, NJ 07647-2485

4. **LEGAL BASIS FOR ANDA SUBMISSION**: 505 j

5. **Supplement(s)**: N/A

6. **PROPRIETARY NAME**: None

7. **NONPROPRIETARY NAME**: Albuterol Sulfate Inhalation Solution

8. **SUPPLEMENT(S) PROVIDE(S) FOR**: N/A

9. **AMENDMENTS AND OTHER DATES:**

Steripak:

02/27/98	Submission of ANDA (received on 03/04/98)
10/09/98	Micro Review Concern.
11/06/98	Major Amendment.
03/17/99	Gratuitous Amendment.
04/13/99	Gratuitous Chemistry Amendment
07/09/99	Fax Amendment.
07/29/99	Gratuitous Micro Amendment
08/20/99	Labeling Amendment
08/30/99	Fax amendment (Chemistry and Microbiology)
09/01/99	NC to Labeling Amendment
10/08/99	**Minor amendment (CMC).**

FDA:

03/17/98	Acknowledgment.
03/17/98	EERs are issued.
05/18/98	Labeling Review 1st w/ Deficiency letter.

07/20/98	Bio-review was completed. It is acceptable.
09/29/98	Major CMC deficiency letter & CMC CR#1.
06/17/99	*FAX CMC deficiency letter* and CMC review #2.
07/21/99	Labeling Review 2nd w/ deficiency letter.
07/19/99	Method Validation Report, with comments.
07/21/99	Micro Review w/ Deficiencies.
08/06/99	NA (Fax) letter and CMC review #3.
09/15/99	Micro review completed–Approved.
09/22/99	NA-Minor, CR#4.

10. **PHARMACOLOGICAL CATEGORY**: Bronchodilator

11. **Rx or OTC**: Rx

12. **RELATED IND/NDA/DMF(s)**:

13. **DOSAGE FORM**: Solution (inhalation)

14. **POTENCY**: 0.083%

15. **CHEMICAL NAME AND STRUCTURE**:
See P. 39 under USP 23 or CR#1 for the name and structure.

16. **RECORDS AND REPORTS**: N/A

17. **COMMENTS**:
- EER pending
- Labeling review is acceptable (08/25/99).
- Bio-review is completed, and it is acceptable (07/20/98).
- Micro review completed-acceptable (09/15/99).
- MV completed, Acceptable. (07/19/99)
- CMC, acceptable (10/14/99)

18. **CONCLUSIONS AND RECOMMENDATIONS**:
Approval. (Pending for EER)

19. **REVIEWER**: Bing Cai, Ph.D. **DATE COMPLETED**: 10/15/99 **DATE Revised**:

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Chemistry Review #5

10/15/79

Page(s) 2

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releasable.

9/22/99

Chemistry Comments

#3

Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **CHEMIST'S REVIEW NO.:** No. 4

2. **ANDA #** 75-343

3. **NAME AND ADDRESS OF APPLICANT:**
Steripak Limited
Goddard Road, Astmoor, Runcorn
Chesire, WA7 1QF, England

U.S. Agent:
Zenith Goldline Pharmaceuticals
U.S. Agent for Steripak Limited
Attention: Jason A. Gross
140 Legand Avenue
Northvale, NJ 07647-2485

4. **LEGAL BASIS FOR ANDA SUBMISSION:** 505 j

5. **Supplement(s):** N/A

6. **PROPRIETARY NAME:** None

7. **NONPROPRIETARY NAME:** Albuterol Sulfate Inhalation Solution

8. **SUPPLEMENT(S) PROVIDE(S) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**
Steripak:

02/27/98	Submission of ANDA (received on 03/04/98)
10/09/98	Micro Review Concern.
11/06/98	Major Amendment.
03/17/99	Gratuitous Amendment.
04/13/99	Gratuitous Chemistry Amendment
07/09/99	Fax Amendment.
07/29/99	***Gratuitous Micro Amendment***
08/20/99	***Labeling Amendment***
08/30/99	***Fax amendment (Chemistry and Microbiology)***

09/01/99 ***NC to Labeling Amendment***

FDA:

03/17/98	Acknowledgment.
03/17/98	EERs are issued.
05/18/98	Labeling Review 1st w/ Deficiency letter.
07/20/98	Bio-review was completed. It is acceptable.
09/29/98	Major CMC deficiency letter.
06/17/99	*FAX CMC deficiency letter*
07/21/99	Labeling Review 2nd w/ Deficiency letter.
07/19/99	Method Validation Report, with comments.
07/21/99	Micro Review w/ Deficiencies.
08/06/99	NA (Fax) letter and CMC review.
09/15/99	Micro review completed-Approved.

10. **PHARMACOLOGICAL CATEGORY**: Bronchodilator

11. **Rx or OTC**: Rx

12. **RELATED IND/NDA/DMF(s)**:
Proventil® (Schering)---Innovator;

13. **DOSAGE FORM**: Solution (inhalation)

14. **POTENCY**: 0.083%

15. **CHEMICAL NAME AND STRUCTURE**:
See P. 39 under USP 23 or CR#1 for the name and structure.

16. **RECORDS AND REPORTS**: N/A

17. **COMMENTS**:
- EER pending for their packaging company,
- Labeling review is acceptable (08/25/99).
- Bio-review is completed, and it is acceptable (07/20/98).
- Micro review completed- acceptable (09/15/99).
- MV completed, suitable but with few comments. (07/19/99)

- Minor CMC deficiencies could be found in item 38.

18. **CONCLUSIONS AND RECOMMENDATIONS:**
Not approvable (Minor Amendment). The firm has already provided 2 FAX amendments.

19. **REVIEWER:**	**DATE COMPLETED:**	**DATE Revised:**
Bing Cai, Ph.D.	09/17/99	09/20/99

Page(s) 14

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Chemistry Review #4

9/20/99

Page(s) 3

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Chemistry Comments.

#3P 8/6/99

Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **CHEMIST'S REVIEW NO.:** No. 3

2. **ANDA #** 75-343

3. **NAME AND ADDRESS OF APPLICANT:**
Steripak Limited
Goddard Road, Astmoor, Runcorn
Chesire, WA7 1QF, England

U.S. Agent:
Zenith Goldline Pharmaceuticals
U.S. Agent for Steripak Limited
Attention: Jason A. Gross
140 Legand Avenue
Northvale, NJ 07647-2485

4. **LEGAL BASIS FOR ANDA SUBMISSION:** 505 j

5. **Supplement(s):** N/A

6. **PROPRIETARY NAME:** None

7. **NONPROPRIETARY NAME:** Albuterol Sulfate Inhalation Solution

8. **SUPPLEMENT(S) PROVIDE(S) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**

Steripak:

02/27/98	Submission of ANDA (received on 03/04/98)
10/09/98	Micro Review Concern.
11/06/98	Major Amendment.
03/17/99	Gratuitous Amendment.
04/13/99	Gratuitous Chemistry Amendment
07/09/99	**Fax Amendment.**
07/29/99	Gratuitous Micro Amendment

FDA:

03/17/98	Acknowledgment.
03/17/98	EERs are issued.
05/18/98	Labeling Review 1st w/ Deficiency letter.
07/20/98	Bio-review was completed. It is acceptable.
09/29/98	Major CMC deficiency letter.
06/17/99	*FAX CMC deficiency letter*

07/21/99 Labeling Review 2nd w/ Deficiency letter.
07/19/99 Method Validation Report, with comments.
07/21/99 Micro Review completed w/ Deficiencies.

10. **PHARMACOLOGICAL CATEGORY:** Bronchodilator

11. **Rx or OTC:** Rx

12. **RELATED IND/NDA/DMF(s):**

13. **DOSAGE FORM:** Solution (inhalation)

14. **POTENCY:** 0.083%

15. **CHEMICAL NAME AND STRUCTURE:**
See P. 39 under USP 23 or CR#1 for the name and structure.

16. **RECORDS AND REPORTS:** N/A

17. **COMMENTS:**
- EER need update.
- Labeling review 2nd round has completed, and labeling has deficiencies (05/18/98).
- Bio-review is completed, and it is acceptable (07/20/98).
- Micro 1st round completed w/ Deficiencies (07/21/99).
- MV completed, suitable but with few comments. (07/19/99)
- Minor CMC deficiencies could be found in item 38.

18. **CONCLUSIONS AND RECOMMENDATIONS:**
Not approvable (Facsimile Amendment).

19. **REVIEWER:**	**DATE COMPLETED:**	**DATE Revised:**
Bing Cai, Ph.D.	08/02/99	08/04/99

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Chemistry Review #3

8/4/99

Page(s) 2

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Chemistry Comments

6/17/99

Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **CHEMIST'S REVIEW NO.:** No. 2

2. **ANDA #** 75-343

3. **NAME AND ADDRESS OF APPLICANT:**

Steripak Limited
Goddard Road, Astmoor, Runcorn
Chesire, WA7 1QF, England

U.S. Agent:
Zenith Goldline Pharmaceuticals
U.S. Agent for Steripak Limited
Attention: Jason A. Gross
140 Legand Avenue
Northvale, NJ 07647-2485

4. **LEGAL BASIS FOR ANDA SUBMISSION:**
505 j

5. **Supplement(s):** N/A

6. **PROPRIETARY NAME:** None

7. **NONPROPRIETARY NAME:** Albuterol Sulfate Inhalation Solution

8. **SUPPLEMENT(S) PROVIDE(S) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**

Steripak:

02/27/98	Submission of ANDA (received on 03/04/98)
10/09/98	Micro Review Concern.
11/06/98	Major Amendment.
03/17/99	Gratuitous Amendment.
04/13/99	Gratuitous Chemistry Amendment

FDA:

03/17/98	Acknowledgment.
03/17/98	EERs are issued.
05/18/98	Labeling Review was completed and Deficiency letter was issued.
07/20/98	Bio-review was completed. It is acceptable.
09/29/98	Major CMC deficiency letter was sent out.

10. **PHARMACOLOGICAL CATEGORY**: Bronchodilator

11. **Rx or OTC**: Rx

12. **RELATED IND/NDA/DMF(s)**:

13. **DOSAGE FORM**: Solution (inhalation)

14. **POTENCY**: 0.083%

15. **CHEMICAL NAME AND STRUCTURE**:
See P. 39 under USP 23 or CR#1 for the name and structure.

16. **RECORDS AND REPORTS**: N/A

17. **COMMENTS**:
- EERs (issued on 3/17/98) for Steripak are acceptable. Additional EER need to be issued for the new proposed packaging company (overwrap), Unipack Ltd. in UK.
- Labeling review is completed, and labeling has deficiencies. No response has received at this time.
- Bio-review is completed, and it is acceptable.
- Micro is pending.
- FAX CMC deficiencies could be found in item 38.

18. **CONCLUSIONS AND RECOMMENDATIONS**:
Not approvable (FAX Amendment).

19. **REVIEWER**:	**DATE COMPLETED**:	**DATE Revised**:
Bing Cai, Ph.D.	04/29/99	05/20/99

Page(s) 22

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Chemistry Review # 2

5/20/99

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Chemistry Comments

12.

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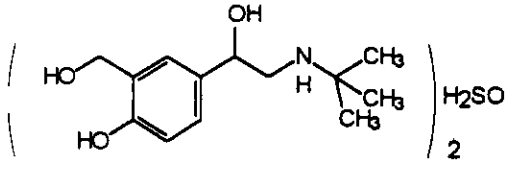
13. DOSAGE FORM: Solution

14. POTENCY: 0.083%

15. CHEMICAL NAME AND STRUCTURE:
See P. 39 under USP 23 for the name.



16. RECORDS AND REPORTS: N/A

17. COMMENTS:
EERs (issued on 3/17/98) for Steripak are acceptable.

Labeling review is completed, and labeling has deficiencies.

Bio-review is completed, and it is acceptable.

Micro is pending.

Major CMC deficiencies could be found in item 38.

18. CONCLUSIONS AND RECOMMENDATIONS:
Not approvable (Major Amendment).

19.

REVIEWER:	DATE COMPLETED:	DATE Revised:
Bing Cai, Ph.D.	07/31/98	8/31/98

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Chemistry Review

8/31/99

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-343

BIOEQUIVALENCE REVIEW(S)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-343 APPLICANT: Zenith Goldline Pharamceuticals

DRUG PRODUCT: Albuterol Sulfate Inhalation Solution
0.083%

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

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,

/S/

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

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-343 APPLICANT: Zenith Goldline Pharamceuticals

DRUG PRODUCT: Albuterol Sulfate Inhalation Solution
0.083%

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

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,

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

Albuterol Sulfate Inhalation Solution
0.083%
ANDA #75-343
Reviewer: Jahnavi S. Kharidia
X:\new\firmsnz\zenith\ltrs&rev\75343w.298

Zenith Goldline Pharmaceuticals
for
Steripak Limited
Goddar Road, Cheshire WA71QF, UK
Submission date:
February 27, 1998

Review of a Waiver Request

Background

The firm is requesting a waiver of *in vivo* bioavailability studies for Albuterol Sulfate Solution for Inhalation, 0.083%. The product is indicated for the relief of bronchospasm in patients with reversible obstructive airway disease and acute attacks of bronchospasm. The reference listed drug is Proventil® 0.083% solution for Inhalation manufactured by Schering. Listed below is the composition of the test and reference products:

Component	Proventil® mg/mL	Test Product mg/mL

Comments

1. Albuterol Sulfate Solution for Inhalation, 0.083%, is a solution dosage form intended for administration by inhalation. The test product has the same active ingredient as the reference. The test product does not contain a preservative because it is intended for single use.

2. Waiver of in-vivo bioequivalence study may be granted under 21 CFR 320.22 (b) (3), which states that the drug products are (i) administered by inhalation as a gas or vapor and (ii) contains an active drug ingredient or therapeutic moiety in the same dosage form as a drug product that is the subject of a approved full NDA.

Recommendation

The Division of Bioequivalence agrees that the information submitted by Zenith Goldline demonstrates that Albuterol Sulfate 0.083% Solution for Inhalation falls under 21 CFR Section 320.22(b)(3) of the Bioavailability/ Bioequivalence Regulations. The waiver of the in-vivo bioequivalence study for 0.083% solution for Inhalation of the test product is granted. The Division of Bioequivalence deems the test product to be bioequivalent to Proventil® 0.083% solution for Inhalation manufactured by Schering.

/S/ /S/ –
Jahnavi S. Khadda
Division of Bioequivalence
Review Branch III

RD INITIALLED BY BDAVIT
FT INITIALLED BY BDAVIT /S/ Date: 7/20/98

Concur: /S/ Date: 7/20/98
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-343

MICROBIOLOGY REVIEW(S)

OFFICE OF GENERIC DRUGS
HFD-620
MICROBIOLOGY REVIEW #2

SUBMISSION:	DOCUMENT DATE:	CDER DATE:	ASSIGNED DATE:
ANDA 75-343a	7/29/99	7/30/99	9/2/99
	8/30/99	8/31/99	

ANDA: 75-343 APPLICANT: Zenith Goldline Pharmaceuticals

DRUG PRODUCT: Albuterol Sulfate Inhalation Solution USP, 0.083%

In reference to your submission dated July 29, 1999 for the above product the submitted MICROBIOLOGY information is acceptable.

Sincerely yours,

/S/

Mary Fanning, M.D., Ph.D.
Associate Director of Medical Affairs
Office of Generic Drugs
Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS
HFD-620
Microbiology Review #2
September 9, 1999

A. 1. **ANDA: 75-343**

APPLICANT: Zenith Goldline Pharmaceuticals
140 Legrand Ave.
Northvale, NJ 07647

US Authorized Agent for:
Steripak Limited
Goddard Road
Astmoor, Runcorn
Chesire WA7IQF
England

2. PRODUCT NAME: Albuterol Sulfate Inhalation Solution USP, 0.083%

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: Inhalation solution, 2.5mg/3mL, single unit dose

4. METHOD(S) OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: Bronchodilator

B. 1. DATE OF INITIAL SUBMISSION: Feb. 27, 1998
(Received March 4, 1998)

2. DATE OF AMENDMENTS:
July 29, 1999 **(Gratuitous Amendment)**
Subject of this Review (Received July 30, 1999)

August 30,1999 **(Amendment to Micro. deficiencies)**
Subject of this Review (Received August 31, 1999)

3. RELATED DOCUMENTS: N/A

4. ASSIGNED FOR REVIEW: September 2,1999

C. REMARKS: The applicant did not respond to deficiency #2 in the July 29,1999 gratuitous amendment. A teleconference was held 9/3/99 with Jason Gross to address the lack of response to

deficiency #2, because the remainder of the submission is acceptable and the microbiology review was holding the application from approval.

Dr. Gross explained that the response to deficiency #2 is contained in the August 30,1999 amendment which was already sent to the agency (which L. Ensor received later to review).

D. CONCLUSIONS: The submission **is recommended** for approval on the basis of sterility assurance. Specific comments regarding the aseptic filling process are provided in "E. Review Notes".

/99

Lynne A. Ensor, Ph. D.

cc:

43a

1/15/99

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Micro Review #2

9/9/99

Page(s) 2

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releasable.

8/6/99

micro Comments #1

OFFICE OF GENERIC DRUGS
HFD-620
Microbiology Review #1
June 21, 1999

A. 1. **ANDA: 75-343**

APPLICANT: Zenith Goldline Pharmaceuticals
140 Legrand Ave.
Northvale, NJ 07647

US Authorized Agent for:
Steripak Limited
Goddard Road
Astmoor, Runcorn
Chesire WA7IQF
England

2. PRODUCT NAME: Albuterol Sulfate Inhalation Solution USP, 0.083%

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: Inhalation solution, 2.5mg/3mL, single unit dose

4. METHOD(S) OF STERILIZATION: **Aseptically filled using blow-fill-seal technology**

5. PHARMACOLOGICAL CATEGORY: Bronchodilator

B. 1. DATE OF INITIAL SUBMISSION: Feb. 27, 1998
Subject of this Review (Received March 4, 1998)

2. DATE OF AMENDMENTS: 4/13/99 - Chemistry amendment
11/6/98
3/17/99 - Chemistry amendment

3. RELATED DOCUMENTS:

4. ASSIGNED FOR REVIEW: June 14,1999

C. REMARKS: The Applicant has informed the Agency (10/9/98 letter) that the ANDAs 75-313, 75-343 and 75-271 are manufactured at the same facility employing the same equipment and similar processes. Also, the Applicant states that the same microbiological information package was provided in each of these applications.

The microbiology review was prepared by reviewing the red jacket (Chemistry) copy (v. 1.1)

and the blue jacket (Archival) copy (v. 1.2, 1.3 & 2.1) of the ANDA.

D. CONCLUSIONS: The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments regarding the aseptic filling process are provided in "E. Review Notes" and a Microbiologist's draft of deficiencies to be provided to the Applicant found at the end of the review.

/S/ 2/21/99
Lynne A. Ensor, Ph. D.

cc:

Page(s) 13

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Micro Review #1

6/6/99

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-343

ADMINISTRATIVE DOCUMENTS

APPROVAL SUMMARY PACKAGE

ANDA NUMBER: 75-343

FIRM: Steripak Limited

U.S. Agent: Zenith Goldline Pharmaceuticals

DOSAGE FORM: Inhalation Solution

STRENGTH: 0.083%

DRUG: Albuterol Sulfate Inhalation Solution

cGMP STATEMENT/EIR UPDATED STATUS: Pending per 10/15/99.

BIO STUDY: Acceptable (waiver is granted) 07/20/98 (vol. 1.1).

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
Acceptable per 07/19/99 (vol. 2.1).

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?
Containers used in the stability studies are identical to those listed in container section.

Expiration dating period is 24 months for the drug product.

LABELING:
Satisfactory per Watkins' review dated 08/25/99 (vol. 2.1).

STERILIZATION VALIDATION (IF APPLICABLE):
Acceptable per 09/15/99, signed off by M. Fanning (vol. 3.1).

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?):

NDS Source: DMF Holder:

Recent DMF updates	Review	Status
08/02/99	Yes	Adequate(08/18/99)

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?)

The manufacture process for stability batches are the same as those for the commercial production.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?
(see above).

Bing Cai
Review Chemist

Mike Smela
Team Leader

Division of Chemistry I
OGD/CDER
10/15/99

cc:

En
F
H
V

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **ANDA 75343/000**
Priority:
Org Code: **600**
Stamp: **04-MAR-1998** Regulatory Due:
Action Goal:
District Goal: **04-MAY-1999**
Applicant: **STERIPAK**
GODDARD RD, ASTMOOR, RUNCORN
CHESIRE, ENGLAND, UK
Brand Name:
Established Name: **ALBUTEROL SULFATE**
Generic Name:
Dosage Form: **SOL (SOLUTION)**
Strength: **0.083%**

FDA Contacts:

M. DILLAHUNT	**(HFD-613)**	**301-827-5846**	**, Project Manager**
B. CAI	**(HFD-620)**	**301-827-5848**	**, Review Chemist**
M. SMELA JR	**(HFD-625)**	**301-827-5848**	**, Team Leader**

Overall Recommendation:

ACCEPTABLE on 03-NOV-1998 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 02-JUN-1998 by M. EGAS (HFD-322) 301-594-0095

Establishment:
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **02-JUN-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **FINISHED DOSAGE STERILITY TESTER**

Establishment:
DMF No
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **17-MAR-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

Establishment:
)MF No:
ADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **03-NOV-1998**
Responsibilities: **DRUG SUBSTANCE OTHER TESTER**

RECORD OF TELEPHONE CONVERSATION

Dr. Lynne Ensor initiated a telecon with Dr. Jason Gross regarding the responses received to the microbiology deficiency letter (faxed to the firm 8/4/99). An amendment containing responses to the microbiology deficiency letter was received by the agency 7/30/99 and is being reviewed by L. Ensor. The firm disregarded to respond to deficiency #2 (regarding WFI exceeded endotoxin contamination levels). The firm said that a response to deficiency #2 was already sent out (may have already been received by the agency) and the reason that it wasn't addressed in the first amendment is because the firm was responding pro-actively to deficiencies that were cited for 2 of their related products (ANDA 75-313 &75-271). The other ANDAs applications were very similar to that submitted for ANDA 75-343 and the firm expected similar deficiencies to those already provided to them for the other applications (which they addressed in the first amendment).

The response to deficiency #2 has been sent to the agency. In addition, Dr. Gross faxed a copy of the response directly to Dr. Ensor for review (the fax was received by Dr. Ensor 8/2/99).

DATE
AUGUST 2, 1999

ANDA NUMBER
75-343

IND NUMBER

TELECON

INITIATED BY
SPONSOR

X FDA

PRODUCT NAME
ALBUTEROL SULFATE INHALATION SOLN., 0.083% (Base)

FIRM NAME

Zenith Goldline Pharmaceuticals

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD

Dr. Jason Gross, Director of Global Regulatory Affairs.

TELEPHONE NUMBER
1(800) 387-0133

SIGNATURE

/S/

9/3/99

CC:

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

ANDA Number: **75-343** Date of Submission: **July 9, 1999**

Applicant's Name: **Steripak Limited**

Established Name: **Albuterol Sulfate Inhalation Solution, 0.083% (base)**

Labeling Deficiencies:

1. UNIT DOSE CONTAINER (3 mL)

   a. Satisfactory.

2. FOIL POUCH (5 x 3 mL)

   a. Satisfactory.

3. CARTON (25's, 30's and 60's)

   a. Satisfactory.

4. PHYSICIAN INSERT

   a. CLINICAL PHARMACOLOGY

      i. Revise "prime" to read "primary" in the first sentence of this section.

      ii. Include the following to appear as the third sentence of paragraph one of this section:

      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.

      iii. Begin a new paragraph with the sentence which begins:

      In vitro studies and...

      iv. Revise sentences four and five of this section to read as follows:

...muscle, date indicate 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.

v. Revise the first sentence of the second paragraph of this section to read as follows:

In controlled clinical trials, albuterol has been shown 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.

vi. Revise the remainder of this section, beginning with the paragraph which begins "Studies in asthmatic patients..." as follows:

The effects of rising doses of albuterol and isoproterenol aerosols were studied in volunteers and asthmatic patients. Results in normal volunteers indicated that the propensity for increase in heart rate for albuterol is 1/2 to 1/4 that of isoproterenol. In asthmatic patients similar cardiovascular differentiation between the two drugs was also seen.

Preclinical: Intravenous studies in rats with albuterol sulfate have demonstrated that albuterol crosses the blood-brain-barrier and reaches brain concentrations that are amounting to approximately 5% of the plasma concentrations. In structures outside the blood-brain barrier (pineal and pituitary glands), albuterol concentrations were found to be 100 times those in the whole brain.

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

Pharmacokinetics: After either IPPB or nebulizer administration in asthmatic patients, less than 20% of a single albuterol dose was absorbed; the remaining amount was recovered from the nebulizer

and apparatus and expired air. Most of the absorbed dose was recovered in the urine 24 hours after drug administration. Following a 3 mg dose of nebulized albuterol, the maximum albuterol plasma level at 0.5 hour was 2.1 ng/mL (range 1.4 to 3.2 ng/mL). It has been demonstrated that the following oral administration of 4 mg of albuterol, the elimination half-life was 5 to 6 hours.

Clinical Trials: In controlled clinical trials, most patients exhibited an onset of improvement in pulmonary function within 5 minutes as determined by FEV_1. FEV_1 measurements also showed that the maximum average improvement in pulmonary function usually occurred at approximately 1 hour following inhalation of 2.5 mg of albuterol by compressor-nebulizer, and remained close to peak for 2 hours. Clinically significant improvement in pulmonary function (defined as maintenance of a 15% or more increase in FEV_1 over baseline values) continued for 3 to 4 hours in most patients and in some patients continued up to 6 hours.

b. INDICATIONS AND USAGE

Revise to read as follows:

…in patients 12 years of age and older with reversible obstructive airway disease and acute attacks of bronchospasm.

c. CONTRAINDICATIONS

Revise to read as follows:

…hypersensitivity to albuterol or any of its components.

d. WARNINGS

Revise this section as follows:

WARNINGS
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 sulfate inhalation solution 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 agents, 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 sulfate inhalation solution can produce paradoxical bronchospasm, which may be life-threatening. If paradoxical bronchospasm occurs, albuterol sulfate inhalation solution should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new vial.

Cardiovascular Effects: Albuterol sulfate inhalation solution, 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 sulfate inhalation solution 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 sulfate inhalation solution, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

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

Microbial Contamination: To avoid microbial contamination, the entire contents of the unit-dose vial should be administered immediately after the vial has been opened for the first time.

c. PRECAUTIONS

i. General

A. Include the following to appear as the last sentence of paragraph one of this subsection:

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.

B. Revise the second paragraph of this subsection to read as follows:

…ketoacidosis. As with other beta-agonist medications, 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 potassium supplementation.

ii. Information for Patients

Revise to read as follows:

Information for Patients: See Illustrated PATIENT'S INSTRUCTIONS FOR USE.
General: The action of albuterol sulfate inhalation solution may last up to 6 hours or longer. Albuterol sulfate inhalation solution should not be used more frequently than recommended. Do not increase the dose or frequency of doses of albuterol sulfate inhalation solution without consulting your physician. If you find that treatment with albuterol sulfate inhalation solution 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 sulfate inhalation solution, 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 the use of albuterol sulfate inhalation solution.

Effective use of albuterol sulfate inhalation solution includes understanding of the way that if should be administered. See illustrated "PATIENT'S INSTRUCTIONS FOR USE".

Microbial Contamination: To avoid microbial contamination, the entire contents of the unit-dose vial should be administered immediately after the vial has been opened for the first time.

Mixing Different Inhalation Solutions: Drug compatibility (physical and chemical), efficacy, and safety of albuterol sulfate inhalation solution when mixed with other drugs in a nebulizer have not been established.

Drug Interactions: Other short-acting sympathomimetic aerosol bronchodilators or epinephrine should not be used concomitantly with albuterol.

Beta Blockers: Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta-agonists, such as albuterol sulfate inhalation solution, 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 the effects is not known, caution is advised in the co-administration of beta-agonists with non-potassium-sparing diuretic.

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 this finding 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.

Monoamine Oxidase Inhibitors or Tricyclic Antidepressants: Albuterol should be administered with extreme caution in 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.

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 and above dietary doses of 2 mg/kg (approximately 2 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). In another study, this effect was blocked by the coadministration of propranolol, a non-selective beta-adrenergic antagonist.

In an 18 month study in CD-1 mice, albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 500 mg/kg (approximately 200 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). In a 22 month study in the Golden Hamster, albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 50 mg/kg (approximately 25 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

Albuterol sulfate was not mutagenic in the Ames test with or without metabolic activation using tester strains *S. typhimurium* TA1537, TA1538, 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.

Reproduction studies in rats demonstated no evidence of impaired fertility at oral doses of albuterol sulfate up to 50 mg/kg (approximately 40 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

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

A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses when albuterol was administered orally at a dose of 50 mg/kg (approximately 80 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

Studies in pregnant rats with tritiated albuterol demonstrated that approximately 10% of the circulating maternal drug is transferred to the fetus. Disposition in the fetal lungs is comparable to maternal lungs, but fetal liver disposition is 1% of the maternal liver levels.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, 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 reported in the offspring of patients being treated with albuterol. Some of the mothers were taking multiple medications during their pregnancies. Because no consistent pattern of defects can be discerned, a relationship between albuterol use and congenital anomalies has not been established.

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

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

Nursing Mothers: It is not…

d. ADVERSE REACTIONS

Revise as follows:
ADVERSE REACTIONS: The results of clinical trials with albuterol sulfate inhalation solution in 135 patients showed the following side effects which were considered probably or possibly drug related:

Percent incidence of Adverse Reactions

Reaction	Percent Incidence
CENTRAL NERVOUS SYSTEM	
Tremors	20%
Dizziness	7%
Nervousness	4%
Headache	3%
Insomnia	1%

GASTROINTESTINAL	
Nausea	4%
Dyspepsia	1%
EAR, NOSE, AND THROAT	
Nasal Congestion	1%
Pharyngitis	<1%
CARDIOVASCULAR	
Tachycardia	1%
Hypertension	1%
RESPIRATORY	
Bronchospasm	8%
Cough	4%
Bronchitis	4%
Wheezing	1%

No clinically relevant laboratory abnormalities related to albuterol sulfate inhalation solution were determined in these studies.

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

e. OVERDOSAGE

Revise to read as follows:

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., angina, hypertension, tachycardia with rates up to 200 beats per minute, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, malaise, and insomnia. In addition, seizures, hypotension, fatigue, and hypokalemia may also occur. As with all sympathomimetic aerosol medications, cardiac arrest and even death may be associated with abuse of albuterol sulfate inhalation solution. Treatment consists of discontinuation of albuterol sulfate inhalation solution 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 sulfate inhalation solution.

The oral median lethal dose of albuterol sulfate in mice is greater than 2000 mg/kg (approximately 810 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). In mature rats, the subcutaneous (sc) median lethal dose of albuterol sulfate is approximately 450 mg/kg (approximately 360 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). In small young rats, the subcutaneous median lethal dose is approximately 2000 mg/kg (approximately 1600 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). The inhalational median lethal dose has not been determined in animals.

f. DOSAGE AND ADMINISTRATION

i. Revise the first sentence to read as follows:

…adults and pediatric patients 12 years of age and…

ii. Revise the third sentence to read as follows:

…albuterol, administer the entire contents…

iii. Include the following to appear as the second paragraph of this section:

Drug compatibility (physical and chemical), efficacy, and safety of albuterol sulfate inhalation solution when mixed with other drugs in a nebulizer have not been established.

iv. Include the following to appear as the last subsection:

Microbial Contamination: To avoid microbial contamination, the entire contents of the unit-dose vial should be administered immediately after the vial has been opened for the first time.

The nebulizer should be cleaned in accordance with the manufacturer's instructions. Failure to do so could lead to bacterial contamination of the nebulizer, and possible infection.

g. HOW SUPPLIED

We note you have submitted carton labeling for a 30 count size in addition to the 25 and 60 count size list ~~in~~ your HOW SUPPLIED section. Please revise and/or comment.

5. PATIENT INSTRUCTIONS FOR USE INSERT

a. Revise the first instruction to read as follows:

…vial and squeeze the entire contents into…

b. Revise the sixth instruction to include the following:

…(see manufacturer's instructions). Failure to clean the nebulizer in accordance with the manufacturer's instructions could lead to bacterial contamination of the nebulizer, and possible infection.

c. Include the following to appear prior to the storage recommendation:

Mixing Compatibility: The safety and effectiveness of albuterol sulfate inhalation solution have not been determined when one or more drugs are mixed with it in a nebulizer. Check with your physician before mixing any medications in your nebulizer.
Microbial Contamination: To avoid microbial contamination, the entire contents of the unit-dose vial should be administered immediately after the vial has been opened for the first time.

Please revise your physician's insert and patient instructions for use labeling, as instructed above, and submit 12 copies of final printed 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.

/S/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Food and Drug Administration

Memorandum

July 19, 1999

Supervisory Chemist, Drug Chemistry Branch
Northeast Regional Laboratory, HFR-NE560

CT: ANDA 75-343: Albuterol Sulfate Inhalation Solution
Zenith Goldline Pharmaceuticals
US Agent for Steripak Limit; Northvale, NJ 07647-2485
Sample No. 59730

Bing Cai, Ph.D., Review Chemist
Office of Generic Drugs, CDER, HFD-625

The analysis of Albuterol Sulfate Inhalation Solution, was performed by the Northeast Regional Laboratory using the firm's method and the samples provided. The following is a summary of the analysis.

ution	Results	Specifications
say:		
ntification:		
lated Substances:		
own degradants		
known degradants/impurities		
tal degradants		

analyst submitted comments concerning the retention times of the mixed standards vs. those the individual impurities, the concentration of a possible degradant and a need to clarify the olution requirements. See analyst's memo for detail on these items.

other analytical problems were encountered with the tests performed. The firm's analytical thod appears to be suitable for regulatory analysis of this product, but, the analyst's comments ould be considered before approval.

/S/

a S. Walker

: HFC-140
HFD-354

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

ANDA Number: **75-343** Date of Submission: **February 27, 1998**

Applicant's Name: **Steripak Limited**

Established Name: **Albuterol Sulfate Inhalation Solution, 0.083% (base)**

Labeling Deficiencies:

1. UNIT DOSE CONTAINER (3 mL)

   a. Include and asterisk(*) following "3 mL" in "2.5 mg/3 mL*".

   b. Include the following statement:

      FOR ORAL INHALATION

2. CARTON (25s and 60s)

   a. Principal Display Panel

      i. Revise the established name to read:

         Albuterol Sulfate Inhalation Solution

      ii. Include the following statement:

         NOT FOR INJECTION

      iii. See comment a under UNIT DOSE CONTAINER.

      iv. Include the following statement:

         PREDILUTED WITH NORMAL SALINE

   b. Top Panel

      See comments under Principal Display Panel.

   c. Replace the "CAUTION: Federal law..." statement with the symbol "Rx only" or "℞ only". We refer

you to the Guidance For Industry, "Implementation of Section 126, Elimination of Certain Labeling Requirements...", at the internet site, **http://www.fda.gov/cder/guidance/index.htm** for guidance.

d. Include the following equivalency statement:

Equivalent to 0.5 mL Albuterol Sulfate).5%* diluted to 3 mL with normal saline.

e. Revise the "Each vial contains..." statement on the 60s count carton to an "Each mL contains..." statement. In addition, revise the statement on both carton sizes to read as follows:

Each mL, for oral inhalation, contains albuterol sulfate equivalent to 0.83 mg albuterol in a sterile...

f. We note "edetate disodium and sodium citrate" are listed as inactive ingredients. However, these ingredients do not appear in your components/composition statement. Please comment and/or revise.

g. Revise to read "Protect from Light".

h. Delete the NDC number. We refer you to 21 CFR 207.35(3)(i).

3. INSERT

I. PHYSICIAN INSERT

a. TITLE

See comment a. i. under CARTON. In addition, revise throughout the text of the insert.

b. DESCRIPTION

i. Chemical name - Revise to read "α" rather than "a".

ii. To be in accord with USP 23, revise the molecular weight to read "576.71" rather than "576.7".

iii. Delete the last sentence of paragraph

five. This information appears in the HOW SUPPLIED section of the insert.

iv. See comment under f under CARTON.

c. CLINICAL PHARMACOLOGY

i. Paragraph one - Replace "/" following "cyclic-3" with a comma in the first sentence.

ii. Paragraph three - Delete the third sentence.

d. WARNINGS

Paragraph two - Insert "sympathomimetic" prior to "nebulizers" in the first sentence.

e. PRECAUTIONS

i. Information for Patients - Delete the penultimate paragraph. This does not appear in the approved labeling of the reference listed drug.

ii. Carcinogenesis, Mutagenesis, Impairment of Fertility - Delete "and" from this subsection heading.

iii. Teratogenic Effects

A) Revise this subsection heading to read as follows:

Pregnancy: Teratogenic Effects, Pregnancy Category C

B) Delete the last three sentences. This does note appear in the approved labeling of the reference listed drug.

iv. Pediatric Use - Revise to read as follows:

...of albuterol sulfate in pediatric patients below the age...

f. DOSAGE AND ADMINISTRATION

i. Revise the third sentence of paragraph one to read as follows:

...albuterol, administer the contents of...

ii. Delete paragraph two. This does not appear in the approved labeling of the reference listed drug.

g. HOW SUPPLIED

Include the following in conjunction with the storage temperature recommendations:

Protect From Light. Retain in carton until time of use.

h. Include the following statement in conjunction with the perforation on the insert:

PHARMACIST - DETACH HERE AND GIVE LOWER PORTION TO PATIENT

II. PATIENT INSTRUCTIONS FOR USE INSERT

a. TITLE

i. See comment a. i. under CARTON. In addition, revise throughout the text of the insert.

ii. Include the following text prior to "Read complete..." statement:

Note: This is a unit-dose vial. No dilution is required.

b. Revise the text of this insert to be in accord with the approved labeling of the reference listed drug. Please utilize the same illustrations and replace "bottle" with "vial".

c. Delete the last sentence of the "Note". This does not appear in the approved labeling of the reference listed drug.

Please revise your unit dose labels, carton and insert labeling, as instructed above, and submit final printed labels and labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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.

_____

Jerry Phillips
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

Unit Dose Container Label:

Unit Dose Carton Label:

Professional Package Insert Labeling:

Patient Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Proventil®

NDA Number: 19-243

NDA Drug Name: Proventil® Inhalation Solution

NDA Firm: Schering-Plough

Date of Approval of NDA Insert and supplement #:
September 7, 1993/S-010
Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Approved proventil labels in file folder.
Basis of Approval for the Carton Labeling: Approved proventil labeling in file folder.

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	
Is this name different than that used in the Orange Book?	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	
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 bioeqivalency 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:*******

We will ask firm to provide more information.

1. **Please note the NDA packages this product in HDPE bottles and the firm wants to package in LDPE vials. Ventolin packages their product in this type of vial but they have a foil wrap. This firm does not propose a foil wrap. Is the foil wrap for moisture, light resistance? Is the carton sufficient for light protection and does this container allow the egress or ingress of materials?**

2. **See comment f under CARTON. Do you concur?** yes. see comment in CMC. section 20.

FOR THE RECORD:

1. Review based on the labeling of the listed drug (PROVENTIL®; Approved September 7, 1993, Revised October 1992).

2. Patent/ Exclusivities:

   There are no patents or exclusivities that pertain to this drug product.

3. Storage/Dispensing Conditions:

   NDA: Store between 2° and 25° C (36° and 77° F).

   ANDA: Store between 2° and 25° C (36° and 77° F). Protect from Direct Sunlight. Retain in Carton Until Time of Use. See comment to firm to revise.

   USP: NOT USP nor NF.

4. Product Line:

   The innovator markets their product in 3 mL HDPE bottles. They are supplied in boxes of 25.

   The applicant proposes to market their product in LDPE vials containing 3 mL. They will supply the vials in cartons of 25s and 60s (the 60s will have 2 boxes of 30s in them).

5. The solution has been accurately described in the HOW SUPPLIED section. See page 491, Vol. 1.2. It is described as a colorless to pale yellow solution.

6. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be inconsistent with the listing of inactive ingredients found in the statement of components and composition appearing on pages 71,72 and 73, Vol. 1.1.

7. All manufacturing will be performed by Steripak for Zenith Goldline Pharmaceuticals Inc. All outside firms are utilized for testing. See pages 152 and 156, Vol. 1.2.

8. Container/Closure:

   This product will be packaged in 3.5 mL LDPE polyethylene blow/fill/seal vials. See page 413, Vol. 1.2.

Date of Review: April 14, 1998

Date of Submission: February 27, 1998

Reviewer: /S/ **Date:** 5/18/98

Team Leader: /S/ **Date:** 5/18/98

---

cc:

A1.L

for March 17, 1998

Application: **ANDA 75343/000**
Stamp: **04-MAR-1998** Regulatory Due:
Applicant: **STERIPAK**
GODDARD RD, ASTMOOR, RUNCOR
CHESIRE, ENGLAND, UK

Priority:
Action Goal:
Brand Name:
Established Name: **ALBUTEROL SULFATE**
Generic Name:
Dosage Form: **SOL (SOLUTION)**
Strength: **0.083%**

Org Code: **600**
District Goal: **04-MAY-1999**

FDA Contacts: **S. OKEEFE** **(HFD-617)** **301-827-5848** **, Project Manager**
M. SMELA JR **(HFD-625)** **301-827-5848** **, Team Leader**

Overall Recommendation:

Establishment:

IF No:
DA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC**
Milestone Date: **17-MAR-1998**

Responsibilities: **FINISHED DOSAGE STERILITY TESTER**

Establishment:

DMF No
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC**
Milestone Date: **17-MAR-1998**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

Establishm

MF No:
ADA No:

Profile: **SNI** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC**
Milestone Date: **17-MAR-1998**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment: **F980071**

DMF No:

AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC**
Milestone Date: **17-MAR-1998**

Responsibilities: **FINISHED DOSAGE STABILITY TESTER**

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-343

CORRESPONDENCE

Zenith Goldline
PHARMACEUTICALS
Regulatory Affairs

Via Federal Express

OCT 8 1999

ORIG AMENDMENT
N/Am

Douglas L. Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT-
Chemistry and Microbiology

RE: ANDA 75-343 - Albuterol Sulfate Inhalation Solution, 0.083% (as Albuterol)

Dear Mr. Sporn:

Reference is made to the Agency's correspondence dated September 22, 1999 (copy provided in Reference), concerning our Abbreviated New Drug Application for the above referenced product. Pursuant to 21 CFR Parts 314.96 and 314.120, we are amending our application by responding to the deficiencies cited in your letter. As stated in your correspondence, this response should be considered a MINOR AMENDMENT.

In response to the Agency's comments, we submit the following:

A. CHEMISTRY DEFICIENCIES

Sincerely,
ZENITH GOLDLINE PHARMACEUTICALS, INC.

Jason A. Gross, Pharm. D.
Director, Global Regulatory Affairs
Authorized US Agent for Steripak Ltd., UK

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Zenith Goldline
PHARMACEUTICALS
Regulatory Affairs

Via Federal Express

NEW CORRESP
NC

Mr. Douglas L. Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESPONDENCE TO LABELING AMENDMENT

RE: ANDA # 75-343 Albuterol Sulfate Inhalation Solution, 0.83% (base)

Dear Mr. Sporn:

Reference is made to our pending abbreviated new drug application for Albuterol Sulfate Inhalation solution, 0.83% (base), and to the Agency's telephone communication of August 25, 1999.

In response to the Agency's telephone communication, Zenith Goldline Pharmaceuticals is providing an additional twelve (12) copies of final printed insert labeling. We trust that the quality of the print on the attached labeling will be satisfactory.

Zenith Goldline Pharmaceuticals has made every effort to ensure that this response is complete and that the information contained herein is satisfactory. Should the Office of Generic Drugs have any questions or require additional information, please contact our office at (201) 767-1700 x239.

Sincerely,
ZENITH GOLDLINE PHARMACEUTICALS, INC.

Jason A. Gross Pharm. D
Director
Global Regulatory Affairs

Attachments

CENTER FOR DRUG EVALUATION RESEARCH
RECD
SEP 01 1999
CDD

140 Legrand Ave., Northvale, New Jersey 07647 • (201) 767-1700 (800) 387-0133 Fax (201) 767-3804

Zenith Goldline
PHARMACEUTICALS
Regulatory Affairs

ORIG AMENDMENT
FA

Via Federal Express

August 30, 1999

Douglas L. Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FACSIMILE AMENDMENT
Chemistry and Microbiology

RE: Albuterol Sulfate Inhalation Solution 0.083% (as Albuterol).
ANDA 75-343

Dear Mr. Sporn:

Reference is made to the Agency's correspondence dated August 6, 1999 (copy provided in Reference), concerning our Abbreviated New Drug Application for the above referenced product. Pursuant to 21 CFR parts 314.96 and 314.120, we are amending our application by responding to the deficiencies cited in your letter. As stated in your correspondence, this response should be considered a FACSIMILE AMENDMENT.

In response to the Agency's comments, we submit the following:

DEFICIENCIES

Page(s) 3

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

8/30/99

IN ADDITION

In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. *Please provide any additional stability data for the new exhibit batch, if available.*

   Response
   The 6 month stability data were supplied in the firm's response to the Agency dated July 9, 1999, as Exhibit 5. There are no further updates to the data, the 9 month time point is due in September

2. *Your response must also address the labeling deficiencies which were provided to you on July 21, 1999*

   Response
   Please note that our response to the labeling deficiencies of 07/21/99 were submitted to the Agency on August 20, 1999, as a Labeling Amendment. We also acknowledge the Agency's telephone communication of 8/25/99 and will provide additional copies of final printed labeling as requested, under separate cover.

3. *The CGMP status of the firms referenced in the ANDA will be evaluated by our Office of Compliance and an adequate evaluation is required prior to approval.*

   Response:
   Steripak Limited acknowledges that the firms referenced in the ANDA relative to the manufacturing and testing of the product must be in compliance with cGMP at the time of approval. Steripak Limited was inspected by the FDA in April 1998 and was found acceptable.

Zenith Goldline has made every effort to ensure that this response is complete and that the information contained herein is satisfactory. Should the Office of Generic Drugs have any questions or require additional information, please contact our office at (201)-767-1700 x239.

Sincerely,

ZENITH GOLDLINE PHARMACEUTICALS, INC.

Jason A. Gross, Pharm. D.
Director, Global Regulatory Affairs
Authorised US Agent for Steripak Ltd., UK

Zenith Goldline
PHARMACEUTICALS
Regulatory Affairs

Via Federal Express

NDA ORIG AMENDMENT

AUG 2 0 1999

Mr. Douglas L. Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

LABELING AMENDMENT

RE: ANDA # 75-343 Albuterol Sulfate Inhalation Solution, 0.83% (base)

Dear Mr. Sporn:

Reference is made to our pending Abbreviated New Drug Application for the above referenced product, and to the Agency's correspondence dated July 21, 1999 (copy attached). Pursuant to 21 CFR Parts 314.96 and 314.120, we are amending our application at this time by responding to the Labeling deficiencies cited in your facsimile.

To facilitate review of this submission, and in accordance with 21 CFR Part 314.94(a)(8)(iv), we have provided side-by-side comparisons of the labeling proposed in this amendment (physician's insert and patient instructions for use insert) versus the last submitted labeling, with all differences annotated and explained. These can be found accompanying the final printed inserts in Exhibit 2 of this amendment.

LABELING DEFICIENCIES:

1. *UNIT-DOSE CONTAINER*
   Satisfactory in final

   Response:
   We note and acknowledge the Agency's approval of our unit-dose containers.

2. *FOIL POUCH*
   Satisfactory in final

   Response:
   We note and acknowledge the Agency's approval of our foil pouches.

3. *CARTON*
   Satisfactory in final

   Response:
   We note and acknowledge the Agency's approval of our cartons.

RECD
AUG 23 1999
OGD
EVALUATION AND RESEARCH

140 Legrand Ave., Northvale, New Jersey 07647 ▪ (201) 767-1700 (800) 387-0133 Fax (201) 767-3804

4. ***PHYSICIAN INSERT***
   - ***a. CLINICAL PHARMACOLOGY***
   - ***b. INDICATIONS AND USAGE***
   - ***c. CONTRAINDICATIONS***
   - ***d. WARNINGS***
   - ***e. OVERDOSAGE***
   - ***f. DOSAGE AND ADMINISTRATION***

   Revise as indicated in Comments 4.a.i. through 4.f.iv.

   Response:
   We have revised our physician insert as instructed in Comments 4.a.i. through 4.f.iv.

   g. ***HOW SUPPLIED***
   We note you have submitted carton labeling for a 30 count size in addition to the 25 and 60 count size list in your HOW SUPPLIED section. Please revise and/or comment.

   Response:
   We respectfully remind the Agency that cartons of 30's are not labeled for individual sale, rather, they are intended for packaging into the cartons of 60's (2 x 30's).

5. ***PATIENT INSTRUCTIONS FOR USE INSERT***
   Revise as indicated in Comments 5.a. through 5.c.

   Response:
   We have revised our patient instructions for use insert as instructed in Comments 5.a. through 5.c.

Zenith Goldline Pharmaceuticals, Inc. has revised their physician's insert and patient instructions for use insert as instructed, and herewith submits twelve (12) copies of final printed labeling.

Zenith Goldline Pharmaceuticals, Inc., notes and acknowledges that the Agency reserves the right to further changes in our labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

This completes our response to the Agency's Labeling Deficiency facsimile dated July 21, 1999. We trust that all outstanding labeling deficiencies have been adequately addressed and look forward to the approval of our Abbreviated New Drug Application.

Sincerely,
ZENITH GOLDLINE PHARMACEUTICALS, INC.

Jason A. Gross Pharm. D
Director
Global Regulatory Affairs

Attachments

Zenith Goldline
PHARMACEUTICALS
Regulatory Affairs

ORIG AMENDMENT
45

Via Federal Express

JUL 29 1999

Mr. Douglas L. Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

GRATUITOUS MICROBIOLOGY AMENDMENT

RE: ANDA 75-343 - Albuterol Sulfate Inhalation Solution, 0.083% (base)

Dear Mr. Sporn:

Reference is made to our pending Abbreviated New Drug Application for the above referenced product. Following receipt of identical microbiology deficiency letters for Steripak's two other pending applications (ANDA 75-313 for Ipratropium Bromide Inhalation Solution, 0.02% and ANDA 75-271 for Cromolyn Sodium Inhalation Solution USP, 1.0%; copies attached in Reference) currently under the Agency's review, we are submitting the enclosed additional information (Exhibits 1 and 2).

The microbiology deficiencies cited in Reference are responded to below:

Page(s) 6

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Information and are not

releasable.

7/29/99

3. *Please clarify the meaning of "biannual basis" as it pertains to your media fill requalification program. This term may mean that requalification is completed either twice annually (without a set period of time between the 2 testing dates), every 6 months (semi-annually) or every 2 years.*

Response

We conduct media simulation studies every 6 months therefore the words "biannual basis" mean occurring twice a year.

This completes our Gratuitous Microbiology Amendment. Please do not hesitate to contact us should you require additional information.

Sincerely,
ZENITH GOLDLINE PHARMACEUTICALS, INC.

Jason A. Gross, Pharm. D.
Director of Global Regulatory Affairs
Authorized US Agent for Steripak Limited, UK

\emc
Attachments

Zenith Goldline
PHARMACEUTICALS

Regulatory Affairs

Via Telefax (301)827-4337 and Federal Express

JUL 9 1999

NDA ORIG AMENDMENT
N/FA

Mr. Douglas L. Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FACSIMILE AMENDMENT – Chemistry, Bioequivalence and Labeling

RE: ANDA 75-343 - Albuterol Sulfate Inhalation Solution, 0.083% (base)

Dear Mr. Sporn:

Reference is made to the Agency's correspondence dated June 17, 1999 (copy provided in Reference), concerning our Abbreviated New Drug Application for the above referenced product. Pursuant to 21 CFR Parts 314.96 and 314.120, we are amending our application by responding to the deficiencies cited in your letter. As stated in your correspondence, this response should be considered a FACSIMILE AMENDMENT.

In response to the Agency's comments, we submit the following:

A. CHEMISTRY DEFICIENCIES

Page(s) 1

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

7/9/99

This completes our Facsimile Amendment response to the Agency's comments of June 17, 1999. We trust that all outstanding deficiencies have been adequately addressed, and look forward to the approval of our Abbreviated New Drug Application.

Sincerely,
ZENITH GOLDLINE PHARMACEUTICALS, INC.

Jason A. Gross, Pharm. D.
Director of Global Regulatory Affairs
Authorized US Agent for Steripak Limited, UK

Attachments

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Zenith Goldline
PHARMACEUTICALS

Regulatory Affairs

Via Federal Express

APR 13 1999

Mr. Douglas L. Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP

GRATUITOUS CHEMISTRY AMENDMENT

RE: Albuterol Sulfate Inhalation Solution USP, 0.083% (base)
ANDA 75-343

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application dated February 27, 1998, our Major Amendment Response dated November 6, 1998, and to our Gratuitous Amendment of March 17, 1999. Further reference is made to the Teleconference held on March 25, 1999, between the FDA and Zenith Goldline Pharmaceuticals, Inc., during which the Agency clarified their position regarding the use of LDPE container systems, with and without secondary foil over-wrap, as it pertains to our products.

At this time, and as we committed to in Attachment #7 of the Gratuitous Amendment of March 17, 1999, we are providing Water Vapor Permeation Test Results (USP23 <661>) for the foil pouches. We respectfully acknowledge Mr. Michael Smela's advisement given during the Teleconference, that the Agency does not require this data, however, since the testing has been conducted, we are submitting it to the FDA as ancillary information.

This completes our Gratuitous Chemistry Amendment. We trust that all outstanding deficiencies have now been adequately addressed, and we look forward to the approval of our Abbreviated New Drug Application.

Sincerely,
ZENITH GOLDLINE PHARMACEUTICALS, INC.

Jason A. Gross, Pharm. D.
Director of State, Federal and
International Regulatory Affairs

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Zenith Goldline
PHARMACEUTICALS

Regulatory Affairs

Via Federal Express

March 17, 1999

ORIG AMENDMENT

AA

Douglas L. Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

GRATUITOUS AMENDMENT

RE: Albuterol Sulfate Inhalation Solution USP, 0.083% (base)
ANDA 75-343 - Chemistry Amendment

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application (ANDA) dated February 27, 1998. Reference is also made to your Major Amendment deficiency letter dated September 29, 1998, and our response to this correspondence dated November 6, 1998.

Pursuant to 21 CFR Parts 314.96 and 314.120, we are hereby providing an additional amendment to our application in order to better meet the agency requirements, specifically we are amending our response to comment #15 of the chemistry deficiencies cited in your September 29, 1998 "Not Approvable" letter.

The following response to Item #15, supercedes that provided November 6, 1998:

CHEMISTRY DEFICIENCIES (*Item #15*)

This completes our Gratuitous Amendment to the agency's chemistry comment #15. We trust that all outstanding deficiencies have been adequately addressed in this amendment and our letter of November 6, 1998; and we now look forward to the approval of our Abbreviated New Drug Application.

Sincerely,
ZENITH GOLDLINE PHARMACEUTICALS, INC.

Jason A. Gross, Pharm. D.
Director of State/Federal and
International Regulatory Affairs

Zenith Goldline
PHARMACEUTICALS

Regulatory Affairs

Via Federal Express

AC

November 6, 1998

Douglas L. Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MAJOR AMENDMENT

RE: Albuterol Sulfate Inhalation Solution, (0.083% as Albuterol)
ANDA 75-343

Dear Mr. Sporn:

Reference is made to the Agency's correspondence dated September 29, 1998 (copy attached), concerning our Abbreviated New Drug Application for the above referenced product. Pursuant to 21 CFR Parts 314.96 and 314.120, we are amending our application by responding to the deficiencies cited in your "Not Approvable" letter. As stated in your correspondence, this response should be considered a MAJOR AMENDMENT.

In response to the Agency's comments, we submit the following:

A. DEFICIENCIES

1. *Please clarify if you have used Edetate Disodium and Sodium Citrate, which are listed in your*

Page(s) 5

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

11/6/98

B. IN ADDITION

In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. *Please provide any additional stability data accrued to date.*

Response:

Steripak Limited acknowledges this request and has included the stability data accrued, to date. The data may be found as Attachment 16.

2. *The cGMP status of the firms referenced in the ANDA will be evaluated by our Office of Compliance and an adequate evaluation is required prior to approval.*

Response:

Steripak Limited acknowledges that the firms referenced in the ANDA relative to the manufacturing and testing of the product must be in compliance with cGMP at the time of approval. Steripak Limited was inspected by the FDA in April 1998 and was found acceptable.

3. *The sterility assurance information is pending review.*

Response:

Steripak Limited acknowledges that the sterility assurance section of the ANDA is pending review, and that comments will be communicated separately upon completion of review.

4. *Your response must also address the labeling deficiencies.*

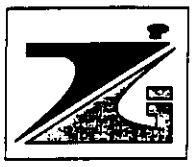
Response

The response herein addresses the Chemistry issues only. Labeling deficiencies are currently being addressed, and the response will be submitted under separate cover.

This completes our Major Amendment response to the Agency's comments of September 29, 1998. We trust that all outstanding deficiencies have been adequately addressed and look forward to the approval of our Abbreviated New Drug Application.

Sincerely,
ZENITH GOLDLINE PHARMACEUTICALS, INC.

Jason A. Gross, Pharm. D.
Director of State, Federal and
International Regulatory Affairs



Zenith Goldline
PHARMACEUTICALS

NAI
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10/16/98

October 9, 1998

Regulatory Affairs

Douglas L. Sporn
Director, Office of Generic Drug (HFD-600)
CDER, FDA
Metro Park North II, Document Room #150
7500 Standish Place
Rockville, MD 20855-2773

Re: Correspondence for the Microbiological Reviewer of:
ANDA 75-343 Albuterol Sulfate Inhalation Solution
ANDA 75-313 Ipratropium Bromide Inhalation Solution
ANDA 75-271 Cromolyn Sodium Inhalation Solution

Dear Mr. Sporn:

Each of the above referenced applications have proceeded through their first review cycles within your office, with two of the applications presently awaiting review of their respective subsequent amendments. We were initially informed that the sterility assurance reviews for each of these ANDA were pending. It our understanding, through follow-up conversations with the appropriate project managers, that the microbiological review queue is long due to limited Agency resources.

It is therefore the purpose of this correspondence is to offer information to the Agency which may alleviate some of the workload as it pertains to the micro-review of the above ANDAs. All three of the subject applications are manufactured at the same facility , utilizing the same equipment and similar processes. It is of special interest that the same microbiological information package was provided in each of these applications.

In light of this information and in order to maximize Agency resources, Zenith Goldline respectfully suggests that the microbiological reviews relevant to our above referenced ANDAs be performed concurrently by one reviewer since the information is identical.

We hope that our recommendation is well received, and serves to assist the Agency in reducing their backlog. Should you have any questions, please contact my office at your convenience.

With best regards,

ZENITH GOLDLINE PHARMACEUTICALS, INC.

Jason A. Gross, Pharm.D.
Director, State, Federal and
International Regulatory Affairs

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OCT 15 1998
GENERIC DRUGS

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Madhu 10-16-98

140 Legrand Ave., Northvale, New Jersey 07647 • (201) 767-1700 (800) 387-0133 Fax (201) 784-1719
Miami, FL • Walton, KY • Cidra, P.R. • St. Croix, U.S. V.I.

ANDA 75-343

MAR 17 1998

Zenith Goldline Pharmaceuticals
U.S. Agent for Steripak Limited
Attention: Jason A. Gross, Pharm D.
140 Legrand Avenue
Northvale, NJ 07647-2485

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 Inhalation Solution, 0.083% (base)

DATE OF APPLICATION: February 27, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: March 4, 1998

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.

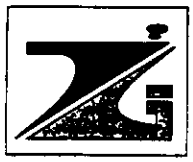
Should you have questions concerning this application, contact:

Sheila O'Keefe
Project Manager
(301) 827-5848

Sincerely yours,

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research



Zenith Goldline
PHARMACEUTICALS

February 27, 1998

Mr. Douglas L. Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20857-2773

RE: ANDA Filing for Albuterol Sulfate Inhalation Solution, 0.083%

Dear Mr. Sporn:

Pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act, and 21 CFR Parts 314.92 and 314.94, Zenith Goldline Pharmaceuticals, Inc., as US Authorized Agent for Steripak Limited, UK, is submitting an Abbreviated New Drug Application for Albuterol Sulfate Inhalation Solution, 0.083%. Steripak Limited and Zenith Goldline Pharmaceuticals, Inc., are wholly owned subsidiaries of IVAX Corporation. In accordance with OGD's Letter to Industry dated December 24, 1996, concerning documentation of agent authorization, a letter from Steripak appointing Zenith Goldline as US Authorized Agent is provided directly following this cover letter.

A Certification Statement, as required by the Generic Drug Enforcement Act of 1992, can be found following the US Agent Authorization letter. In accordance with 21 CFR Part 314.94(d)(5), Zenith Goldline Pharmaceuticals, Inc., is providing a Field Copy of the technical section of this application for submission by CDER to the appropriate FDA district field office. Our Field Copy Certification is provided in the section following the Generic Drug Enforcement Act Certification.

This Abbreviated New Drug Application has been prepared in accordance with OGD's Guidance for Industry, dated April 1997. The Archival Copy, contained in the blue jackets, consists of three (3) volumes, labeled as Volume 1 through Volume 3. Volume 1 of the Archival Copy includes a waiver request for the requirement to submit Bioavailability/Bioequivalence Data. The Review Copy is divided into two parts. The first part, contained in the red jackets, consists of three (3) volumes, labeled as Volume 1 through Volume 3, and includes the Chemistry, Manufacturing and Controls Technical Section. The second part, contained in the orange jacket, consists of one (1) volume, labeled as Volume 3a, and includes a waiver request for the requirement to submit Bioavailability/Bioequivalence Data, and other related information.

Accompanying this application are:

- Sterility Assurance Report #SAR-004 (Section XI and separately bound desk copy), in accordance with OGD's Letter to Industry dated August 4, 1993.
- Three separately bound copies of the Methods Validation.

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In support of this application, Steripak Limited has manufactured Albuterol Sulfate Inhalation Solution, 0.083%, exhibit (test) batch no. 7C2001, 700L. This batch was manufactured and fully packaged in compliance with Policy and Procedure Guide #22-90.

As an overview, and to facilitate review, an "Executive Summary", describing key aspects of this application, immediately precedes the Table of Contents.

Pursuant to Section 5 USC Part 552(b)(4) of the Freedom of Information Act and 21 CFR Part 20.61, regarding privileged and confidential information, we declare that information on Albuterol Sulfate Inhalation Solution, 0.083%, as to its composition, method of manufacture, and test methods constitute trade secrets and confidential commercial information under the law, and are, therefore, not disclosable under the Freedom of Information Act.

We respectfully request a review of this application at your earliest convenience.

Sincerely,

ZENITH GOLDLINE PHARMACEUTICALS, INC.

Jason A. Gross, Pharm. D.
Director, Regulatory Affairs
US Authorized Agent for Steripak Limited, UK

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/KRSB

Attachments