CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

75-664

Generic Name: Albuterol Sulfate Inhalation Solution, 0.5% (base)

Sponsor: Nephron Pharmaceuticals Corporation

Approval Date: June 26, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 75-664

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-664

APPROVAL LETTER

ANDA 75-664

JUN 26 2001

Nephron Pharmaceuticals Corporation
Attention: Steve F. Simmons
4121 34th Street
Orlando, FL 32811

Dear Sir:

This is in reference to your abbreviated new drug application dated July 2, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Albuterol Sulfate Inhalation Solution, 0.5% (base), packaged in 2.5 mg/0.5 mL Unit of-Use Vials.

Reference is also made to your amendments dated April 30, May 15, and May 31, 2001.

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, 0.5% (base) to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Proventil® Solution for Inhalation 0.5% (base), of Schering Corporation).

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

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

We request that you submit, in duplicate, any proposed advertising or promotional copy which 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/

Gary Buehler 6/26/01
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-664

Final Printed Labeling

FRONT

BACK

Scan Area

Albuterol Sulfate
Inhalation Solution, 0.5%*

2.5 mg/0.5 mL*

*Potency expressed as albuterol.

DILUTE BEFORE USE

SEE BACK OF POUCH FOR COMPLETE INSTRUCTIONS.

FOR ORAL INHALATION ONLY

One Single 0.5 mL Sterile Unit-Of-Use Vial

Rx only

Patient's Instructions For Use

Read complete instructions carefully before using.

1. Twist open the top of one albuterol sulfate inhalation solution unit-of-use container (Figure 1).
2. Squeeze the solution into the nebulizer reservoir through the appropriate opening (Figure 2).
3. Add 2.5 mL of sterile normal saline solution, as your doctor has directed.
4. Gently swirl the nebulizer to mix the contents and connect it with the mouthpiece or face mask (Figure 3).
5. Connect the nebulizer to the compressor.
6. Sit in a comfortable, upright position; place the mouthpiece in your mouth (Figure 4) (or put on the face mask); and turn on the compressor.
7. Breathe as calmly, deeply, and evenly as possible until no more mist is formed in the nebulizer chamber (about 5 to 15 minutes). At this point, the treatment is finished.
8. Clean the nebulizer (see manufacturer's instructions).

Please consult your doctor before use. Do not exceed recommended dose.

Figure 1

Figure 2

Figure 3

Figure 4

nephron pharmaceuticals corporation
Orlando, Fl. 32811

Rev. 11-04-09

4. Gently swirl the nebulizer to mix the contents and connect it with the mouth piece or face mask (Figure 3).

Figure 3

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8. Clean the nebulizer (see manufacturer's instructions).

Please consult your doctor before use.

Do not exceed recommended dose.

Manufactured by:
nephron pharmaceuticals corporation
Orlando, FL, 32811

rev. 4-24-01

NDC 0487-9901-30

[redacted]

2.5 mg / 0.5 mL*

*Potency expressed as albuterol.

FOR ORAL INHALATION ONLY
DILUTE BEFORE USE

SEE BACK OF POUCH FOR COMPLETE INSTRUCTIONS.

Each 0.5 mL unit-of-use vial contains 2.5 mg albuterol as the sulfate in an aqueous solution; sulfuric acid is used to adjust the pH between 3 and 5. Contains no preservatives.

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

Please consult your physician before use.

Do not exceed recommended dosage.

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

Discard if solution becomes discolored.

(Note: Albuterol Sulfate Inhalation Solution is a clear, colorless to light yellow solution.)

JUN 26 2001 Rx only APPROVED

STERILE

One 0.5 mL Unit-of-Use Vial

Bar Code

Patient's Instructions For Use

Read complete instructions carefully before using.

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Figure 1

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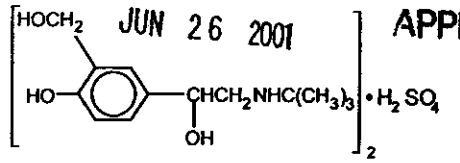
Figure 2

3. Add 2.5 mL of sterile normal saline solution, as your doctor has directed.

[redacted]

DESCRIPTION Albuterol Sulfate Inhalation Solution contains albuterol sulfate, USP, the racemic form of albuterol and a relatively selective $beta_2$-adrenergic bronchodilator. Albuterol sulfate has the chemical name α^1-[(*tert*-Butylamino)methyl]-4-hydroxy-*m*-xylene-α,α'-diol sulfate (2:1) (salt) and the following chemical structure:



The molecular weight of albuterol sulfate is 576.7, and the empirical formula is $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$. Albuterol sulfate is a white crystalline powder, soluble in water and slightly soluble in ethanol. The World Health Organization's recommended name for albuterol base is salbutamol.

Albuterol Sulfate Inhalation Solution, 0.5%, is in concentrated form. Dilute 0.5 mL of the solution to 3 mL with sterile normal saline solution prior to administration.

Each 0.5 mL unit-of-use vial contains 2.5 mg of albuterol (as 3.0 mg of albuterol sulfate, USP) in a sterile, aqueous solution; sulfuric acid is used to adjust the pH to between 3 and 5. Albuterol sulfate inhalation solution contains no sulfiting agents or preservatives. It is supplied in 0.5 mL unit-of-use vials.

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

CLINICAL PHARMACOLOGY The primary action of beta-adrenergic drugs, including albuterol, is to stimulate adenyl cyclase, the enzyme that catalyzes the formation of cyclic-3',5'-adenosine monophosphate (cyclic AMP) from adenosine triphosphate (ATP) in beta-adrenergic cells. 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 ECG 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 ½ to ¼ that of isoproterenol . In asthmatic patients similar cardiovascular differentation 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 5.0% of the plasma concentrations. In structures outside the brain barrier (pineal and pituitary glands), albuterol concentrations were found to be 100 times those in the whole brain.

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines were administered concurrently. The 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 3.0 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 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.

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PHARMACIST: DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

PATIENT'S INSTRUCTIONS FOR USE

Albuterol Sulfate Inhalation Solution, 0.5%*

*Potency expressed as albuterol

Note: The Albuterol Sulfate Inhalation Solution is concentrated and must be diluted.

Read complete instructions carefully before using.

1. Twist open the top of one Albuterol Sulfate Inhalation Solution unit-of-use container (Figure 1).

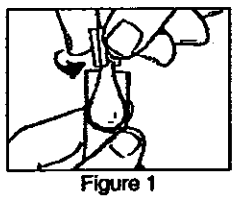

Figure 1

3

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 re-evaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids.

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

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 urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema.

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 in individual patients and could be expected to occur in some patients after use of any beta-adrenergic bronchodilator.

Large doses of intravenous albuterol have been reported to aggravate pre-existing 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: 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 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 use of Albuterol Sulfate Inhalation Solution. Effective use of Albuterol Sulfate Inhalation Solution includes an understanding of the way it should be administered. See illustrated **Patient's Instructions for Use.**

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 nonpotassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with nonpotassium-sparing diuretics.

Digoxin: Mean decreases of 16% to 22% in serum digoxin levels were demonstrated after single-dose intravenous and oral administration of albuterol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical significance of 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 to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of albuterol on the vascular system may be potentiated.

Carcinogenesis, Mutagenesis, and 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 nonselective beta-adrenergic antagonist.

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PHARMACIST: DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

PATIENT'S INSTRUCTIONS FOR USE (continued)

2. Squeeze the solution into the nebulizer reservoir through the appropriate opening (Figure 2).

Figure 2

3. Add 2.5 mL of diluting fluid -- sterile normal saline solution (as your doctor has directed).

4. Gently swirl the nebulizer to mix the contents and connect it with the mouthpiece or face mask (Figure 3).

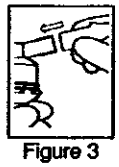

Figure 3

In an 18-month study in CD-1 mice, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 500 mg/kg (approximately 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 of 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 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 an mg/m^2 basis).

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 an sc 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 an sc dose of 0.025 mg/kg (corresponding to less than the maximum recommended daily inhalation dose for adults on an 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 titrated 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: 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 $beta_2$-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 inhalation solution and solution for inhalation in children below the age of 12 years have not been established.

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

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 titrated 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: 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$_2$-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 inhalation solution and solution for inhalation in children below the age of 12 years have not been established.

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

PHARMACIST: DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

PATIENT'S INSTRUCTIONS FOR USE (continued)

5. Connect the nebulizer to the compressor.

6. Sit in a comfortable, upright position; place the mouthpiece in your mouth. (Figure 4)(or put on the face mask); and turn the compressor on.

Figure 4

7. Breathe as calmly, deeply, and evenly as possible until no more mist is formed in the nebulizer chamber (about 5 to 15 minutes). At this point, the treatment is finished.

8. 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.

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 an 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 an mg/m^2 basis,). In small young rats, the sc 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.

DOSAGE AND ADMINISTRATION The usual dosage for adults and pediatric patients 12 years of age and older is 2.5 mg of albuterol (one unit-of-use vial) administered 3 to 4 times daily by nebulization. More frequent administration or higher doses are not recommended. To administer 2.5 mg of albuterol, dilute 0.5 mL of the 0.5% solution for inhalation to a total volume of 3 mL with sterile normal saline solution and administer by nebulization. The flow rate is regulated to suit the particular nebulizer so that 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.

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, 0.5%, is a clear, colorless to light yellow solution, and is supplied in plastic sterile unit-of-use vials of 0.5 mL each, supplied in individual foil pouches:

NDC 0487-9901-30 carton of 30 vials

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

rev. 4-24-01

nephron
pharmaceuticals
corporation
Orlando, FL 32811

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.

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NDC 0487-9901-30 carton of 30 vials

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

rev. 4-24-01

nephron pharmaceuticals corporation
Orlando, FL 32811

PHARMACIST: DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

PATIENT'S INSTRUCTIONS FOR USE (continued)

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 solution for inhalation have not been determined when one or more drugs are mixed with it in a nebulizer.

Store Albuterol Sulfate Inhalation Solution, 0.5%, between 2° and 25° C (36° and 77° F).

ADDITIONAL INSTRUCTIONS: _____

_____

_____

_____

rev. 4-24-01

nephron pharmaceuticals corporation
Orlando, FL 32811

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-664

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 75-664

3. NAME AND ADDRESS OF APPLICANT

Nephron Pharmaceuticals Corp.
4121 34th Street
Orlando, FL 32811-6458

4. LEGAL BASIS FOR SUBMISSION

Accepted by OGD

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Albuterol Sulfate

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

July 2, 1999	Original Submission
September 3, 1999	New Correspondence (response to the Review Support Branch's letter of August 13, 1999)
September 3, 1999	New Correspondence (request for informal meeting to discuss proposed packaging of the drug product)
February 3, 2000	New Correspondence (Agenda for scheduled meeting)
February 16, 2000	New Correspondence (Change the RLD from Ventolin by Glaxo Corp. to Proventil by Schering Plough)
July 20, 2000	Amendment (Microbiology issues & additional stability data)

10. PHARMACOLOGICAL CATEGORY

Beta-adrenergic drug for relief of bronchospasm

11. Rx or OTC

Rx

12. RELATED NDA/DMF(s)

NDA 19-243 Proventil®, Schering Plough
DMF [redacted]
DMF [redacted]
DMF [redacted]

13. DOSAGE FORM

Solution

14. POTENCY

0.5% (2.5 mg/0.5 mL)

15. CHEMICAL NAME AND STRUCTURE

See USP 24, page 55.

16. RECORDS AND REPORTS

N/A

17. COMMENTS

N/A

18. CONCLUSIONS AND RECOMMENDATIONS

This ANDA is not approvable. Inform the applicant of deficiencies listed in item 38 of the review.

19. REVIEWER:

/S/

/Shirley S. Brown

DATE COMPLETED:

10/4/00

September 22, 2000

APPEARS THIS WAY
ON ORIGINAL

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Chemistry Closed

1. **CHEMISTRY REVIEW NO.** 2

2. **ANDA #** 75-664

3. **NAME AND ADDRESS OF APPLICANT**

Nephron Pharmaceuticals Corp.
4121 34th Street
Orlando, FL 32811-6458

4. **LEGAL BASIS FOR SUBMISSION**

Accepted by OGD

5. **SUPPLEMENT(s)**

N/A

6. **PROPRIETARY NAME**

N/A

7. **NONPROPRIETARY NAME**

Albuterol Sulfate

8. **SUPPLEMENT(s) PROVIDE(s) FOR:**

N/A

9. **AMENDMENTS AND OTHER DATES:**

July 2, 1999	Original Submission
September 3, 1999	New Correspondence (response to the Review Support Branch's letter of August 13, 1999)
September 3, 1999	New Correspondence (request for informal meeting to discuss proposed packaging of the drug product)
February 3, 2000	New Correspondence (Agenda for scheduled meeting)
February 16, 2000	New Correspondence (Change the RLD from Ventolin by Glaxo Corp. to Proventil by Schering Plough)
July 20, 2000	Amendment (Microbiology issues & additional stability data)
January 12, 2001	NC (request meeting to discuss microbiology deficiency)
February 12, 2001	Amendment (Microbiology issues)
*March 29, 2001	Amendment (response to October 12, 2000 deficiencies)
*April 17, 2001	Telephone Amendment (response to April 17, 2001 telecon)

*subject of this review

10. **PHARMACOLOGICAL CATEGORY**

11. **Rx or OTC**

Beta-adrenergic drug for relief of bronchospasm

Rx

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

NDA 19-243 Proventil®, Schering Plough
DMF
DMF
DMF

13. **DOSAGE FORM**

Solution

14. **POTENCY**

0.5% (2.5 mg/0.5 mL)

15. **CHEMICAL NAME AND STRUCTURE**

See USP 24, page 55.

16. **RECORDS AND REPORTS**

N/A

17. **COMMENTS**

Response: Per the March 29, 2001 Amendment.

1. Noted.

2. Noted.

18. **CONCLUSIONS AND RECOMMENDATIONS**

Chemistry closed.

The microbiologist's review of the 2/12/01 and 3/29/01 submissions for sterility assurance, and the labeling review of the 3/29/01 submission are pending.

19. **REVIEWER:**

/S/
Shirley S. Brown

DATE COMPLETED:

April 23, 2001
April 6, 2001 (March 29, 2001 amendment)
April 11, 2001 (revised)
April 23, 2001 (April 17, 2001 telephone amendment)

Micro unacceptable 5/4/01
5/8/01
/S/

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CHEMISTRY REVIEW NO. 3

ANDA # 75-664, Albuterol Sulfate Inhalation Solution, 0.5% manufactured by Nephron Pharmaceuticals Corp.

Chemist's Review #2 recommended approval for CMC issues. There have been no changes in the application since. An NA (Minor) issued on 5/11/01 for micro issues. See CR#2 for summary of CMC controls. DMF ---- has had no new submissions. The micro amendment of 5/15/01 and labeling amendments of 4/30 and 5/31/01 have been reviewed.

1. The May 29, 2001 microbiologist's review for the May 15, 2001 submission for sterility assurance concluded that the application is recommended for approval on the basis of sterility assurance.
2. The labeling review for the April 30, 2001 submission requested final print for containers and carton labels. The June 11, 2001 labeling review for the May 31, 2001 submission is an approval summary for FPL.

The ANDA is approvable.

REVIEWER: **DATE COMPLETED:**

Shirley S. Brown June 18, 2001

cc:
ANDA 75-664
ANDA DUP
DIV FILE
Field Copy

Endorsements:

/S/ 6/25/01

HFD-625/Sbrown/6/18/01
HFD-625/Msmela/6/18/01

/S/ 6/25/01

V:\FIRMSNZ\NEPHRON\LTRS&REV\75664r#2.ad2

F/T by: DJ 6/19/01

APPROVABLE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-664

MICROBIOLOGY REVIEW

OFFICE OF GENERIC DRUGS, HFD-620
Microbiology Review #1
December 4, 2000

3.1

A. 1. **ANDA** 75-664

APPLICANT: Nephron Pharmaceuticals Corporation
4121 34th Street
Orlando, FL 32811

2. PRODUCT NAME: Albuterol Sulfate Inhalation Solution 0.5%

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 0.5% sterile inhalation solution in a 1 mL unit-of-use

4. METHOD(S) OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: Bronchodilator

B. 1. DATE OF INITIAL SUBMISSION: February 16, 2000
Subject of this Review (Received February 17, 2000)
Refuse-to-Receive: August 13, 1999 for July 2, 1999

2. DATE OF GRATUITOUS AMENDMENT: July 20, 2000
Subject of this Review (Received July 21, 2000)

3. RELATED DOCUMENTS:
DMF
DMF
DMF

4. ASSIGNED FOR REVIEW: November 15, 2000

C. REMARKS: The subject drug Albuterol Sulfate Inhalation Solution 0.5% is manufactured by Nephron Pharmaceuticals Corporation of Orlando, Florida. The subject drug product is

D. CONCLUSIONS: The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments regarding the [redacted] process are provided in "E. Review Notes" and "Microbiology Comments to be Provided to the Applicant".

/S/ 12/15/00

Marla Stevens-Riley, Ph.D.

/S/ 12/19/00

cc: Original **ANDA**
Duplicate ANDA
Division Copy
Field Copy
Drafted by M. Stevens-Riley, HFD-600 v:microrev\75-664
Initialed by M. Fanning/A. High

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OFFICE OF GENERIC DRUGS, HFD-620
Microbiology Review #2
April 11, 2001

A. 1. **ANDA** 75-664

APPLICANT: Nephron Pharmaceuticals Corporation
4121 34th Street
Orlando, FL 32811

2. PRODUCT NAME: Albuterol Sulfate Inhalation Solution 0.5%

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 0.5% sterile inhalation solution in a 1 mL unit-of-use [redacted]

4. METHOD(S) OF STERILIZATION: [redacted] Form/Fill/Seal technology

5. PHARMACOLOGICAL CATEGORY: Bronchodilator

B. 1. DATE OF INITIAL SUBMISSION: February 16, 2000 (Received February 17, 2000)

2. DATE OF AMENDMENT: March 29, 2001
Subject of this Review (Received March 30, 2001)

3. RELATED DOCUMENTS: None

4. ASSIGNED FOR REVIEW: April 3, 2001

C. REMARKS: The subject amendment provides for the response to the Microbiology Deficiencies dated December 4, 2000.

D. CONCLUSIONS: The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments regarding the [redacted] process are provided in "E. Review Notes" and "Microbiology Comments to be Provided to the Applicant".

/S/ 5/4/01
Marla Stevens-Riley, Ph.D.

/S/ 5/4/01

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5.1

OFFICE OF GENERIC DRUGS, HFD-620
Microbiology Review #3
May 29, 2001

A. 1. **ANDA 75-664**

APPLICANT: Nephron Pharmaceuticals Corporation
4121 34th Street
Orlando, FL 32811

2. PRODUCT NAME: Albuterol Sulfate Inhalation Solution 0.5%

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 0.5% sterile inhalation solution in a 1 mL unit-of-use

4. METHOD(S) OF STERILIZATION: Form/Fill/Seal technology

5. PHARMACOLOGICAL CATEGORY: Bronchodilator

B. 1. DATE OF INITIAL SUBMISSION: February 17, 2000

2. DATE OF AMENDMENT: May 15, 2001
Subject of this Review (Received May 16, 2001)

3. RELATED DOCUMENTS: none

4. ASSIGNED FOR REVIEW: May 25, 2001

C. REMARKS: The subject amendment provides for the response to the Microbiology deficiencies dated May 11, 2001.

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

/S/ 5/31/01
Marla Stevens-Riley, Ph.D

/S/ 5/31/01

cc: Original **ANDA**
Duplicate ANDA
Division Copy
Field Copy
Drafted by M. Stevens-Riley, HFD 600 v:microrev\75-664a2.doc
Initialed by M. Fanning/A. High

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-664

BIOEQUIVALENCE REVIEW

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-664 SPONSOR : Nephron Pharmaceuticals

DRUG AND DOSAGE FORM : Albuterol Sulfate, Inhalation Solution

STRENGTH(S) : 0.5%
TYPES OF STUDIES : Waiver
CLINICAL STUDY SITE(S) : N/A
ANALYTICAL SITE(S) : N/A

STUDY SUMMARY : See Review

DISSOLUTION : See Submission

DSI INSPECTION STATUS

Inspection needed: YES / NO	Inspection status:	Inspection results:
First Generic _____ New facility _____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Andre Jackson BRANCH : I

INITIAL : /S/ DATE : 3/20/2000

TEAM LEADER : Y.C. Huang BRANCH : I

INITIAL : /S/ DATE : 3/20/2000

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : /S/ DATE : 4/3/00

Albuterol Sulfate
Inhalation Solution USP 0.5%
ANDA # 75-664
Reviewer: Andre Jackson
V:\Firmsnz\Ltr&rev\Nephron\75664W.200

Nephron Pharmaceuticals
Orlando, Fl.
Submission Date:
February 16, 2000

Review of a Waiver Request

BACKGROUND

1. The firm has requested a waiver of *in vivo* bioequivalence study requirements for its drug product, Albuterol Sulfate Inhalation Solution, USP, 0.5% based on CFR 320.22(b)(3). The reference listed drug (RLD) is Proventil® Inhalation Solution, multiple-unit container, 0.5% manufactured by Schering Plough, ANDA # 19243.

2. The drug is indicated for the relief of bronchospasm in patients with reversible obstructive airway disease and acute attacks of bronchospasm.

FORMULATION COMPARISON

Components and composition of the test and the reference products are as follows:

Comparison of Formulations		
Ingredient	Test Product (g/L)	RLD (g/L)
Albuterol Sulfate, USP[a]	6.03	6.00
Benzalkonium Chloride	----	
Sulfuric Acid NF	To adjust pH	To adjust pH

[a]Equivalent to 0.5% albuterol as per label claim (i.e., 98.5-101%)

COMMENTS

1. The drug is classified "AN" in the list of the "Approved Drug Products with Therapeutic Equivalence Evaluation".

2. The test drug product contains the same active and inactive ingredients (i.e., water and sulfuric acid) in the same concentrations as the approved listed reference product Proventil®, and is intended for administration by oral inhalation only.

3. The product is a unit-of-use container designed for immediate use therefore the [redacted] which is used as a [redacted], is not required.

3. The waiver of *in vivo* bioequivalence study requirements may be granted based on 21 CFR § 320.22(b)(3) of the Bioavailability/Bioequivalence Regulations.

APPEARS THIS WAY ON ORIGINAL

RECOMMENDATION

The Division of Bioequivalence agrees that the information submitted by Nephron Pharmaceuticals, demonstrates that its Albuterol Sulfate Inhalation Solution, USP, 0.5% falls under 21 CFR § 320.22(b)(3) of Bioavailability/Bioequivalence Regulations. The waiver of *in vivo* bioequivalence study for Albuterol Sulfate Inhalation Solution, USP, 0.5% of the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems Nephron's Albuterol Sulfate Inhalation Solution, USP, 0.5% to be bioequivalent to the reference listed product, Proventil® Inhalation Solution, USP, 0.5%.

Andre Jackson /S/
Division of Bioequivalence
Review Branch I

RD INITIALLED YHUANG /S/
FT INITIALLED YHUANG /S/ Date: 3/20/2000

Concur /S/ Date: 4/3/00

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
cc: ANDA# 75-664 (original, duplicate), HFD-650(Director), HFD-652 (Huang, Jackson), Drug File, Division File.

BIOEQUIVALENCY COMMENTS

ANDA: #75-664 APPLICANT: Nephron Pharmaceuticals

DRUG PRODUCT: Albuterol Sulfate Inhalation Solution USP, 0.5%

The Division of Bioequivalence has completed its review of your application 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

CC: ANDA #75-664
ANDA DUPLICATE
DIVISION FILE
HFD-650/Bio Secretary-Bio Drug File
HFD-652/A. Jackson

Endorsements:
HFD-652/A. Jackson
HFD-652/YC Huang
HFD-650/D. Conner

V:\Firmsn3\Ltr&rev\Nephron\75664W.200

BIOEQUIVALENCY - ACCEPTABLE Submission Date: 02/16/2000

WAIVER (WAI) o/c Strength: 0.5%
Outcome: AC

Outcome Decisions: Acceptable
AC - Acceptable

WINBIO COMMENTS: The waiver is granted

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

(1)

ANDA # : 75-664 SPONSOR : Nephron Pharmaceuticals

DRUG AND DOSAGE FORM : Albuterol Sulfate, Inhalation Solution

STRENGTH(S) : 0.5%
TYPES OF STUDIES : Waiver
CLINICAL STUDY SITE(S) : N/A
ANALYTICAL SITE(S) : **N/A**

STUDY SUMMARY : See Review

DISSOLUTION : See Submission

DSI INSPECTION STATUS

Inspection needed: YES / NO	Inspection status:	Inspection results:
First Generic _____	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER : Andre Jackson BRANCH : I

INITIAL : /S/ DATE : 3/20/2000

TEAM LEADER : Y.C. Huang BRANCH : I

INITIAL : /S/ DATE : 3/20/2000

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : /S/ DATE : 4/3/00

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Active Ingredient Search Results from "Rx" table for query on "albuterol."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
073045	AB	No	ALBUTEROL	Aerosol, Metered; Inhalation	0.09MG/INH	ALBUTEROL	ALPHARMA
018473	AB	Yes	ALBUTEROL	Aerosol, Metered; Inhalation	0.09MG/INH	VENTOLIN	GLAXO WELLCOME
072273	AB	No	ALBUTEROL	Aerosol, Metered; Inhalation	0.09MG/INH	ALBUTEROL	MEDEVA PHARMS MA
074072	AB	No	ALBUTEROL	Aerosol, Metered; Inhalation	0.09MG/INH	ALBUTEROL	MEDISOL
073272	AB	No	ALBUTEROL	Aerosol, Metered; Inhalation	0.09MG/INH	ALBUTEROL	NORTON WATERFORD
017559	BN	No	ALBUTEROL	Aerosol, Metered; Inhalation	0.09MG/INH	PROVENTIL	SCHERING
020503		Yes	ALBUTEROL SULFATE	Aerosol, Metered; Inhalation	EQ 0.09MG BASE/INH	PROVENTIL-HFA	3M
019489		Yes	ALBUTEROL SULFATE	Capsule; Inhalation	EQ 0.2MG BASE	VENTOLIN ROTACAPS	GLAXO WELLCOME
073533	AN	No	ALBUTEROL SULFATE	Solution; Inhalation	EQ 0.083% BASE	ALBUTEROL SULFATE	ALPHARMA
075050	AN	No	ALBUTEROL SULFATE	Solution; Inhalation	EQ 0.5% BASE	ALBUTEROL SULFATE	BAUSCH AND LOMB
072652	AN	No	ALBUTEROL SULFATE	Solution; Inhalation	EQ 0.083% BASE	ALBUTEROL SULFATE	DEY
019773	AN	Yes	ALBUTEROL SULFATE	Solution; Inhalation	EQ 0.083% BASE	VENTOLIN	GLAXO WELLCOME
019269	AN	Yes	ALBUTEROL SULFATE	Solution; Inhalation	EQ 0.5% BASE	VENTOLIN	GLAXO WELLCOME
075063	AN	No	ALBUTEROL SULFATE	Solution; Inhalation	EQ 0.083% BASE	ALBUTEROL SULFATE	HI TECH PHARMA
074543	AN	No	ALBUTEROL SULFATE	Solution; Inhalation	EQ 0.5% BASE	ALBUTEROL SULFATE	HI TECH PHARMA
074880	AN	No	ALBUTEROL SULFATE	Solution; Inhalation	EQ 0.083% BASE	ALBUTEROL SULFATE	NEPHRON
019243	AN	Yes	ALBUTEROL SULFATE	Solution; Inhalation	EQ 0.083% BASE	PROVENTIL	SCHERING
019243	AN	Yes	ALBUTEROL	Solution;	EQ 0.5%	PROVENTIL	SCHERING

			SULFATE	Inhalation	BASE		
074454	AA	No	ALBUTEROL SULFATE	Syrup; Oral	EQ 2MG BASE/5ML	ALBUTEROL SULFATE	ALPHARMA
019621	AA	Yes	ALBUTEROL SULFATE	Syrup; Oral	EQ 2MG BASE/5ML	VENTOLIN	GLAXO WELLCOME
074749	AA	No	ALBUTEROL SULFATE	Syrup; Oral	EQ 2MG BASE/5ML	ALBUTEROL SULFATE	HI TECH PHARMA
018062	AA	Yes	ALBUTEROL SULFATE	Syrup; Oral	EQ 2MG BASE/5ML	PROVENTIL	SCHERING
073419	AA	No	ALBUTEROL SULFATE	Syrup; Oral	EQ 2MG BASE/5ML	ALBUTEROL SULFATE	TEVA
075262	AA	No	ALBUTEROL SULFATE	Syrup; Oral	EQ 2MG BASE/5ML	ALBUTEROL SULFATE	UDL
073165	AA	No	ALBUTEROL SULFATE	Syrup; Oral	EQ 2MG BASE/5ML	ALBUTEROL SULFATE	WATSON LABS
019604	BC	Yes	ALBUTEROL SULFATE	Tablet, Extended Release; Oral	EQ 4MG BASE	VOLMAX	MURO
019604		Yes	ALBUTEROL SULFATE	Tablet, Extended Release; Oral	EQ 8MG BASE	VOLMAX	MURO
019383	BC	No	ALBUTEROL SULFATE	Tablet, Extended Release; Oral	EQ 4MG BASE	PROVENTIL	SCHERING
072629	AB	No	ALBUTEROL SULFATE	Tablet; Oral	EQ 2MG BASE	ALBUTEROL SULFATE	DANBURY PHARMA
072630	AB	No	ALBUTEROL SULFATE	Tablet; Oral	EQ 4MG BASE	ALBUTEROL SULFATE	DANBURY PHARMA
072151	AB	No	ALBUTEROL SULFATE	Tablet; Oral	EQ 2MG BASE	ALBUTEROL SULFATE	GENEVA PHARMS
072152	AB	No	ALBUTEROL SULFATE	Tablet; Oral	EQ 4MG BASE	ALBUTEROL SULFATE	GENEVA PHARMS
019112	AB	No	ALBUTEROL SULFATE	Tablet; Oral	EQ 2MG BASE	VENTOLIN	GLAXO WELLCOME
019112	AB	No	ALBUTEROL SULFATE	Tablet; Oral	EQ 4MG BASE	VENTOLIN	GLAXO WELLCOME
072859	AB	No	ALBUTEROL SULFATE	Tablet; Oral	EQ 2MG BASE	ALBUTEROL SULFATE	LEDERLE
072860	AB	No	ALBUTEROL SULFATE	Tablet; Oral	EQ 4MG BASE	ALBUTEROL SULFATE	LEDERLE
073120	AB	No	ALBUTEROL SULFATE	Tablet; Oral	EQ 2MG BASE	ALBUTEROL SULFATE	MD PHARM
073121	AB	No	ALBUTEROL SULFATE	Tablet; Oral	EQ 4MG BASE	ALBUTEROL SULFATE	MD PHARM
072636	AB	No	ALBUTEROL SULFATE	Tablet; Oral	EQ 2MG BASE	ALBUTEROL SULFATE	MUTUAL PHARM

072637	AB	No	ALBUTEROL SULFATE	Tablet; Oral	EQ 4MG BASE	ALBUTEROL SULFATE	MUTUAL PHARM
072893	AB	No	ALBUTEROL SULFATE	Tablet; Oral	EQ 2MG BASE	ALBUTEROL SULFATE	MYLAN
072894	AB	No	ALBUTEROL SULFATE	Tablet; Oral	EQ 4MG BASE	ALBUTEROL SULFATE	MYLAN
072779	AB	No	ALBUTEROL SULFATE	Tablet; Oral	EQ 2MG BASE	ALBUTEROL SULFATE	NOVOPHARM
072780	AB	No	ALBUTEROL SULFATE	Tablet; Oral	EQ 4MG BASE	ALBUTEROL SULFATE	NOVOPHARM
017853	AB	No	ALBUTEROL SULFATE	Tablet; Oral	EQ 2MG BASE	PROVENTIL	SCHERING
017853	AB	Yes	ALBUTEROL SULFATE	Tablet; Oral	EQ 4MG BASE	PROVENTIL	SCHERING
072316	AB	No	ALBUTEROL SULFATE	Tablet; Oral	EQ 2MG BASE	ALBUTEROL SULFATE	SIDMAK LABS NJ
072317	AB	No	ALBUTEROL SULFATE	Tablet; Oral	EQ 4MG BASE	ALBUTEROL SULFATE	SIDMAK LABS NJ
072619	AB	No	ALBUTEROL SULFATE	Tablet; Oral	EQ 2MG BASE	ALBUTEROL SULFATE	TEVA
072938	AB	No	ALBUTEROL SULFATE	Tablet; Oral	EQ 2MG BASE	ALBUTEROL SULFATE	TEVA
072620	AB	No	ALBUTEROL SULFATE	Tablet; Oral	EQ 4MG BASE	ALBUTEROL SULFATE	TEVA
072939	AB	No	ALBUTEROL SULFATE	Tablet; Oral	EQ 4MG BASE	ALBUTEROL SULFATE	TEVA
072764	AB	No	ALBUTEROL SULFATE	Tablet; Oral	EQ 2MG BASE	ALBUTEROL SULFATE	WATSON LABS
072765	AB	No	ALBUTEROL SULFATE	Tablet; Oral	EQ 4MG BASE	ALBUTEROL SULFATE	WATSON LABS
020291		Yes	ALBUTEROL SULFATE; IPRATROPIUM BROMIDE	Aerosol, Metered; Inhalation	EQ 0.09MG BASE/INH; 0.018MG/INH	COMBIVENT	BOEHRINGER INGELHEIM
020837		Yes	LEVALBUTEROL HYDROCHLORIDE	Solution; Inhalation	EQ 0.021% BASE	XOPENEX	SEPRACOR
020837		Yes	LEVALBUTEROL HYDROCHLORIDE	Solution; Inhalation	EQ 0.042% BASE	XOPENEX	SEPRACOR

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Search results from the "Rx" table for query on "019269."

Active Ingredient:	ALBUTEROL SULFATE
Dosage Form;Route:	Solution; Inhalation
Proprietary Name:	VENTOLIN
Applicant:	GLAXO WELLCOME
Strength:	EQ 0.5% BASE
Application Number:	019269
Product Number:	002
Approval Date:	Jan 16, 1987
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	AN
Patent and Exclusivity Info for this product:	Click Here

Thank you for searching the Electronic Orange Book!

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Patent and Exclusivity Search Results from query on 019269 002.

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

Exclusivity Data

There is no unexpired exclusivity for this product.

Thank you for searching the Electronic Orange Book

Patent and Exclusivity Terms

Return to Electronic Orange Book Home Page

26-JUL-1999 NDAs/Documents in APPLICATION for Criteria:
(appl_no = '019269' AND product_no = '002')

NDA #	Sponsor/Applicant	Address	HFD
N019269	GLAXO WELLCOME	5 MOORE DR/RESEARCH TRIANGLE PARK/NC/27709/US	570

Supporting Applications

NDA #	Drug Name (COMIS)	Established Name (COMIS)
N017853	PROVENTIL TABLETS	

Product	TEq	Rx/OTC	Trade Name (DPRF)	Plastic
002	AN	RX	VENTOLIN	N

Received	Approval	Discontinued	Withdrawal	Current Status	Disc Flag	Ref Drug	Pub Flag
19-APR-84	APPEF/16-JAN-87	/	/	/		Y	Y

Part	Dosage(s)	Route(s) of Administration
01	SOLUTION	INHALATION

Ingredient	Potency	Type
ALBUTEROL SULFATE	EQ 0.5% BASE	ACTIVE
BENZALKONIUM CHLORIDE		INACTIVE
SULFURIC ACID	ADJUST PH	INACTIVE
	QS	INACTIVE

Memo 6/24/99

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8/5/99 email
8/13/27 email
11/10/99 email

Redacted 8

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Printed by Gregory Davis

Electronic Mail Message

ity: COMPANY CONFIDENTIAL

Date: 29-Nov-1999 03:11pm
From: John Grace
GRACEJ
Dept: HFD-613 MPN2 200N
Tel No: 301-827-5846 FAX 301-443-3847

TO: See Below
Subject: Re: Naphron's albuterol

Attached are Nephron's and Ventolin's patient instructions.

Distribution:

TO: Gary Buehler		(BUEHLER)
TO: Robert West		(WESTR)
TO: William Rickman		(RICKMAN)
TO: Nasser Mahmud		(MAHMUDN)
TO: Gregory Davis		(DAVISG)
TO: Donald Hare		(HARE)
CC: Doug Sporn		(SPORND)
CC: Rita Hassall		(HASSALLR)
CC: KIM E DETTELBACH	(OC)	(KDETTELB@OC.FDA.GOV)

APPEARS THIS WAY
ON ORIGINAL

Patient's Instructions For Use

Read complete instructions carefully before using.

1. Twist open the top of one albuterol sulfate inhalation solution unit-of-use container (Figure 1).

Figure 1

2. Squeeze the solution into the nebulizer reservoir through the appropriate opening (Figure 2).

3. Add 2.5 mL of sterile normal saline solution, as your doctor has directed.

Figure 2

4. Gently swirl the nebulizer to mix the contents and connect it with the mouthpiece or face mask (Figure 3).

5. Connect the nebulizer to the compressor.

6. Sit in a comfortable, upright position; place the mouthpiece in your mouth (Figure 4) (or put on the face mask); and turn on the compressor.

Figure 3

7. **Breathe as calmly, deeply, and evenly as possible until no more mist is formed in the nebulizer chamber (about 5 to 15 minutes). At this point, the treatment is finished.**

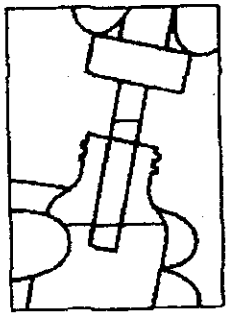
8. Clean the nebulizer (see manufacturer's instructions).

Figure 4

Please consult your doctor before use. Do not exceed recommended dose.

nephron pharmaceuticals corporation
Orlando, FL 32811

Patient's Instructions for Use



Fiaure 1

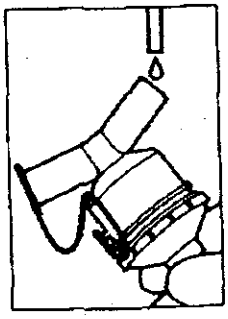


Figure 2

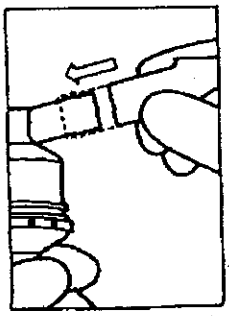


Figure 3

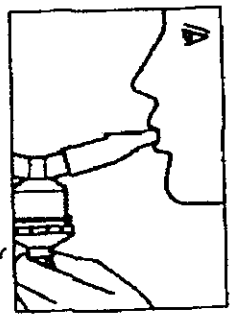


Figure 4

Read complete instructions carefully before using.

1. Draw 0.5 mL of Ventolin Inhalation Solution into the specially marked dropper that comes with each multi-dose bottle (figure 1).

2. Squeeze the solution into the nebulizer reservoir through the appropriate opening (Figure 2).

3. Add 2.5 mL of sterile normal saline solution, as your physician has directed.

4. Gently swirl the nebulizer to mix the contents and connect it with the mouth-piece or face mask (Figure 3).

5. Connect the nebulizer to the compressor.

6. Sit in a comfortable, upright position; place the mouthpiece in your mouth (Figure 4) (or put on the face mask); and turn on the compressor.

(continued)

7. 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 treat-ment is finished.

8. Clean the nebulizer (see manufacturer's instructions).

Please consult your physician before use. Do not exceed recom-mended dose.

NSN 6505-01-257-9953

Allen Hanburys
Division of Glaxo Inc.
Research Triangle Park,
NC 27709
Manufactured in England

11/29/99 email

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Electronic Mail Message

Date: 19-Jan-2000 11:53am
From: Dettelbach, Kim
KDettelb@OC.FDA.GOV
Dept:
Tel No:

TO: Davis, Gregory S (DAVISG@A1)

Subject: nephron albuterol

Assuming that there is no longer a safety concern, I believe the different directions for use based on different packaging configurations are a permissible difference due to difference in manufacturer. Accordingly, assuming there are no other obstacles to approval, the product should be eligible for approval as an ANDA. Please let me know if you have any questions. Thanks.

APPEARS THIS WAY
ON ORIGINAL

Printed by Gregory Davis

Electronic Mail Message

Date: 12-Nov-1999 09:26am
From: Donald Hare
HARE
Dept: HFD-604 MPN2 286
Tel No: 301-827-5845 FAX 301-594-0183

TO: See Below
Subject: Nephron

Doug:

Les Hendeles sent me an article entitled "Bronchoconstrictor Additives in Bronchodilator Solutions" published in the August 1999 J Allergy Clin Immunol. I think it is Les's way of saying that the advantage of a preservative free inhalation solution outweighs the potential safety concerns of approving a unit of use preservative free albuterol sulfate solution 0.5% that needs dilution before administration. I will circulate the article.

Don

Distribution:

TO: Doug Sporn	(SPORND)
CC: Mary Buehler	(BUEHLER)
CC: Rita Hassall	(HASSALLR)
CC: Cecelia Parise	(PARISEC)
CC: John Grace	(GRACEJ)
CC: Gregory Davis	(DAVISG)
CC: Frank Holcombe	(HOLCOMBE)
CC: William Rickman	(RICKMAN)

Greg Davis

Asthma M-69

Bronchoconstrictor additives in bronchodilator solutions

Michael J. Asmus, PharmD, James Sherman, MD, and Leslie Hendeles, PharmD

Gainesville, Fla

Nebulized bronchodilator solutions are available in the United States as both nonsterile and sterile-filled products. Sulfites, benzalkonium chloride (BAC), or chlorobutanol are added to nonsterile products to prevent bacterial growth, but there have been reports of contaminated solutions containing preservatives. Ethylenediamine tetraacetic acid (EDTA) is added to some products to prevent discoloration of the solution. With the exception of chlorobutanol, all of these additives are capable of inducing bronchospasm in a concentration-dependent manner. However, it is rarely apparent to the patient or health care provider that the additive diminishes the bronchodilator effects. Older products (eg, isoproterenol and isoetharine) contain enough sulfites to produce bronchospasm in most patients with asthma, even in those without a prior history of sulfite sensitivity. Bronchoconstriction from inhaled BAC is cumulative, prolonged, and correlates directly with basal airway responsiveness. The multidose dropper bottle of albuterol contains 50 μg BAC/dose, which is below the threshold for bronchoconstriction whereas the screwcap unit-dose vial contains 300 μg/dose, which is above the threshold for many patients. If the screwcap product is used in the emergency department, a patient could receive as much as 1800 μg of BAC in the first hour. Three sterile-filled unit dose albuterol products contain no additives, whereas a fourth, (manufactured by Dey Laboratories) contains 300 μg of EDTA, which is also below the threshold dose for bronchoconstriction. Only additive-free sterile solutions should be used for hourly or continuous nebulization of albuterol. The multidose dropper bottle or the Dey product can be used when the interval between doses is longer, whereas the screwcap product should not be used for acute therapy. Ipratropium is available only as a sterile, additive-free unit-dose vial, as is levalbuterol. (J Allergy Clin Immunol 1999;104:S53-60.)

Key words: Preservatives, sulfites, benzalkonium, bronchodilators, albuterol

Nebulized bronchodilators are commonly used in the treatment of asthma and chronic obstructive pulmonary disease. Administration with a nebulizer is preferred in some clinical situations because it allows passive delivery of medication to the airways. Currently in the United States, the list of nebulized bronchodilators includes the β_2-selective adrenergic agonists (ie, albuterol and bitolterol), the less β_2-selective adrenergic agonists (ie, metaproterenol and isoetharine), the nonselective adrenergic agonists (ie, isoproterenol and racemic epinephrine), and the anticholinergic bronchodilator ipratropium. In addition to this already lengthy list, a nebulized formulation of an albuterol stereoisomer, levalbuterol has recently been approved by the Food and Drug Administration (FDA).

Abbreviations used

BAC:	Benzalkonium chloride
Na-MBS:	Sodium metabisulfite
ED:	Emergency Department
FDA:	Food and Drug Administration
ICU:	Intensive Care Unit
NIH:	National Institutes of Health

Although the safety and efficacy of nebulized bronchodilators is well established, cases of unintended bronchoconstriction have been frequently reported.[1-10] Ironically, certain pharmaceutical properties (eg, osmolality and acidity) as well as the presence of chemical additives such as preservatives and stabilizers in nebulized solutions can cause unwanted bronchoconstriction.[11-15] In this article, the bronchoconstrictor potential of preservatives and stabilizers in nebulized bronchodilator solutions is reviewed, and recommendations for product selection are provided.

PRESERVATIVES AND ADDITIVES

Currently in the United States, approximately one half of nebulized bronchodilator solutions are manufactured as sterile-filled single dose products. The FDA has proposed that all nebulizer solutions should be manufactured sterile,[16] but at least one manufacturer is attempting to prevent this. Most of these solutions contain the active agent, an isotonic aqueous base such as 0.9% sodium chloride, plus hydrochloric or sulfuric acid to adjust the pH. Acidic aerosols can cause bronchoconstriction in asthmatic individuals in direct proportion to the hydrogen ion concentration; however, marked increase in airway resistance is likely to occur only when the pH is less than 2.[17,18] Most nebulized solutions are acidified to pH of approximately 4 to extend the shelf life of the active component.[11] Therefore they are unlikely to cause bronchoconstriction as the result of pH alone. Both hypotonic[19,20] and hypertonic[21,22] aerosols can produce bronchoconstriction as well. However, isotonic solutions will rarely cause appreciable bronchoconstriction, even if they become hypertonic during nebulization due to evap-

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0091-6749/99 $8.00 + 0 1/0/99341

TABLE I. Seldom used nebulized bronchodilator solutions available in the United States

Product	Type	Manufacturer	Dose (drug concentration %)	Additive/Dose*
Metaproterenol	Multidose dropper bottle	Boehringer Ingelheim Morton Grove	15 mg/0.3 ml (5)	BAC† 75 μg BAC
	Unit-dose sterile-filled vial	Boehringer Ingelheim Alpharma Dey Roxane	10 mg/2.5 ml (0.4)	EDTA† 1250 μg EDTA
		Boehringer Ingelheim Alpharma Dey Roxane	15 mg/2.5 ml (0.6)	EDTA† 1250 μg EDTA
Isoetharine	Multidose dropper bottle	Sanofi Winthrop Roxane	5 mg/0.5 ml (1)	2000 μg Na-Bisulfite 50 μg EDTA 390 μg Na-Sulfite 305 μg Na-Bisulfite
Isoproterenol	Multidose dropper bottle	Sanofi Winthrop	2.5 mg/0.5 ml (0.5)	1500 μg Na-Metabisulfite 2500 μg Chlorobutanol
Isoproterenol	Multidose dropper bottle	Sanofi Winthrop	2.5 mg/ 0.25 ml (1)	750 μg Na-Metabisulfite 1250 μg Chlorobutanol
Racemic Epinephrine	Multidose dropper Bottle	Menely & James Nephron	5.6 mg / 0.25 ml (2.25)	300 μg Na-Metabisulfite 50 μg K-Metabisulfite 1250 μg Chlorobutanol 125 mg Benzoic Acid

*Additive content obtained from package insert or communication with manufacturer.
†The manufacturer refused to provide concentrations to the authors, claiming that the additive concentration was proprietary. Because generic equivalents to Alupent were approved by the FDA with an "AN" rating, it is likely that the multidose dropper bottle of metaproterenol manufactured by Boehringer Ingelheim contains 75 mg BAC/dose and the unit-dose vial probably contains 1250 mg EDTA/dose.

orative loss of the diluent.[11] A common additive in sterile and nonsterile inhalation solutions alike is ethylenediamine tetraacetic acid (EDTA). EDTA is present to chelate metallic ions, such as iron, that discolor the solution and cannot be removed during the manufacturing process. EDTA does not inhibit microbial growth. Nonsterile inhalation products may also contain benzalkonium chloride (BAC) or chlorobutanol to inhibit microbial growth, or one of the various sulfites to prevent oxidation.

Sulfites

Salts of bisulfite and metabisulfite are used as antioxidants in a few rarely used bronchodilator solutions including isoproterenol, isoetharine, and racemic epinephrine (Table I). The multidose vial of injectable epinephrine, which is sometimes used in place of or to supplement nebulized therapy, also contains a metabisulfite. Despite an abundance of asthmatic and anaphylaxis-like reactions associated with their use,[14] sulfite-containing solutions such as isoetharine continue to be available and are used by a few institutions to save money. Racemic epinephrine is commonly prescribed for acute obstruction of the upper airway.

The characteristics of airway response to inhaled sulfites have been well documented.[23-26] Wright et al[26] enrolled 30 patients with asthma and 16 healthy volunteers to determine the dose-response, reproducibility, and time course of sodium metabisulfite (Na-MBS)-induced bronchospasm. Subjects inhaled doubling doses of Na-MBS at 3-minute intervals and performed spirometry 2 minutes after each dose. On another day, histamine bronchoprovocation was performed. The main outcome measures were FEV_1 and the provocative dose of histamine or Na-MBS that caused a 20% drop in FEV_1 (PD_{20} FEV_1). Only 1 of 16 healthy nonasthmatic volunteers responded to Na-MBS bronchoprovocation. This finding that subjects without asthma are infrequently affected by the presence of sulfite preservatives is in agreement with other reports.[23-25] In contrast, bronchospasm developed in all 30 subjects with asthma from Na-MBS inhalation challenge. The Na-MBS dose-response was steep and did not appear to plateau. The mean Na-MBS PD_{20} FEV_1 in subjects with asthma was 3.03 μmol (0.58 mg). There was no correlation between histamine PD_{20} FEV_1 and Na-MBS PD_{20} FEV_1. The response to Na-MBS was highly reproducible, as there were no significant difference between mean PD_{20} FEV_1 values for challenges conducted on separate days. The onset of Na-MBS–induced bronchoconstriction was rapid and reached a maximum effect on FEV_1 within 2 minutes after challenge. Unaided recovery from sulfite challenge was also swift, with a majority of FEV_1 values returning spontaneously to 90% of baseline within 30 minutes. When the Na-MBS PD_{20} dose was administered as a single dose, the fall in FEV_1 was significantly greater than when this dose was administered as aliquots at 3-minute intervals, indicating that doses of Na-MBS do not act cumulatively. Moreover, Na-MBS does not appear to enhance airway responsiveness to histamine 1 hour after Na-MBS administration. The mean histamine PD_{20} FEV_1 was 0.74 μmol in 10 subjects 1 hour after Na-MBS challenge compared with a mean of 0.65 μmol ($P > .05$) for histamine

TABLE II. Commonly used nebulized bronchodilator solutions available in the United States

Product	Type	Manufacturer	Dose (drug concentration %)	Additive/dose*
Albuterol	Multidose dropper bottle	Schering-Plough	2.5 mg/0.5 ml (0.5)	50 μg BAC
		Glaxo-Welcome		
		Bausch and Lomb		
		Copley		
		Hi Tech Pharmaceutical		
	Unit-dose non-sterile screwcap vial	Schering-Plough	2.5 mg/3 ml (0.083)	300 μg BAC
		Warrick		
	Unit-dose sterile-filled vial	Dey	2.5 mg/3 ml (0.083)	300 μg EDTA
		Alpharma	2.5 mg/3 ml (0.083)	None
		Glaxo-Welcome		
		Nephron		
Bitolterol	Multidose dropper bottle	Dura	2.5 mg/1.25 ml (0.2)	Alcohol†
Levalbuterol	Unit-dose sterile-filled vial	Sepracor	1.25 mg/3 ml (0.042)	None
			0.63 mg/3 ml (0.021)	None
Ipratropium	Unit-dose sterile-filled vial	Boehringer Ingelheim	0.5 mg/2.5 ml (0.02)	None
		Dey		
		Roxane		

*Additive content obtained from package insert or communication with manufacturer.
†Aqueous vehicle containing 25% ethyl alcohol (50 proof).

challenges performed on another day without Na-MBS pretreatment. In a subset of 10 subjects with asthma, response to Na-MBS was not refractory 60 minutes after a previous Na-MBS challenge. Mean sulfite PD_{20} FEV_1 was 4.07 μmol compared with a mean of 5.39 μmol after a 1 hour recovery period (not significantly different).

Sulfites continue to be available in 50 to 2500 μg quantities in a few bronchodilator solutions (Table I). These quantities would correspond to roughly 1.6 to 7.9 μmol Na-MBS per dose of bronchodilator. Doses of Na-MBS from 0.22 to 12.8 μmol are known to cause at least a 20% decrease in FEV_1 within 2 minutes in patients with asthma.[26] Therefore the amount of sulfite contained in a single dose of bronchodilator (1.6 to 7.9 μmol) is certainly within the range known to cause significant bronchoconstriction. However, it is important to note the pharmacologic effects of the bronchodilator may be able to compensate for constriction caused by the sulfite in patients with mild resting bronchospasm. The FEV_1 of 6 asthmatic subjects sensitive to sulfite inhalation challenge returned to baseline after treatment with nebulized isoetharine containing 0.6 mg/mL Na-MBS.[24] Isoetharine appeared to compensate for bronchoconstriction induced by Na-MBS after a single nebulizer treatment. However, in subjects with more severe airway obstruction, it is likely that the weak bronchodilator effects of isoetharine would not compensate for the sulfite-induced bronchoconstriction.[7] Given that there are β_2-selective agonists such as albuterol that do not contain sulfites, there is no rationale for using sulfite containing bronchodilator solutions to treat bronchospasm.

BAC

BAC is the most common preservative in nebulizer solutions. It is one of several quaternary ammonium compounds used in pharmaceuticals as an antiseptic and disinfectant. It was formerly used as a disinfectant in hospitals (Zephiran, Sanof: Winthrop, New York, N.Y.). Related agents include cetylpyridium chloride and domiphen bromide, antiseptic agents available in a number of mouthwash products. BAC is the bactericidal agent in all nonsterile multidose nebulized solutions of albuterol and metaproterenol as well as the nonsterile screwcap unit-dose albuterol nebulizer solutions (Table II and Fig 1). Additionally, pharmacist-compounded inhalant solutions of albuterol, ipratropium, or cromolyn from bulk chemical grade powder include BAC because they are generally not compounded or packaged in a sterile manner. BAC concentrations of greater than 5 μg/mL are known to promote the release of histamine from mast cells in vitro,[27] but this is unlikely to be the only mechanism of BAC-induced bronchospasm because subjects with greater airway hyperresponsiveness are more susceptible to BAC-induced bronchospasm.

Concern that BAC might be responsible for provoking bronchoconstriction initially came from reports that isotonic ipratropium bromide inhalation solution containing 0.25 mg/mL BAC and 0.5 mg/mL EDTA caused a 20% drop in FEV_1 in 6 of 22 subjects with asthma.[28] This formulation was previously available outside the United States; the US formulation of ipratropium has always been preservative-free. When these 6 subjects received inhalation challenge with increasing concentrations of BAC, it was discovered that BAC produced a dose-dependent bronchoconstriction, which, unlike sulfite-induced bronchospasm, did not resolve spontaneously within 1 hour. The mean concentration of BAC that provoked a 20% drop in FEV_1 (PC_{20} FEV_1) was 0.3 mg/mL (range 0.13 to 2.0 mg/mL). The bronchoconstrictor effects of BAC have been demonstrated in patients with asthma who have had no prior history of unintended bronchoconstriction.[29,30]

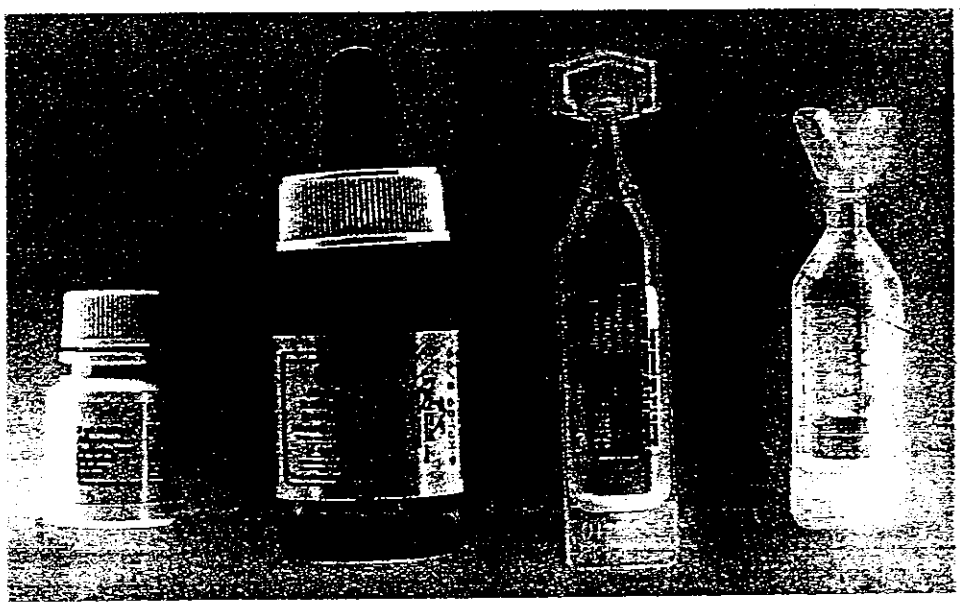

FIG 1. Bronchoconstrictor additive content of commercially available albuterol products for nebulization *(left to right)*. The nonsterile unit-dose screwcap vial (manufactured by Schering-Plough/Warrick) contains 300 μg of BAC per 2.5 mg dose of albuterol. The nonsterile multidose dropper bottle (manufactured by Schering-Plough, Glaxo-Welcome, Bausch and Lomb, Copley, and Hi Tech Pharmaceuticals) contains 50 μg of BAC in each 2.5 mg dose of albuterol. The sterile unit-dose vial (manufactured by Dey Laboratories) contains 300 μg of EDTA per 2.5 mg dose of albuterol. Other sterile unit-dose vials (manufactured by Alpharma, Glaxo-Welcome, and Nephron) contain no additives in each 2.5 mg dose of albuterol.

The nature of the pharmacodynamic response to inhaled BAC in patients with asthma has been well documented. Twenty-eight patients with asthma inhaled doubling doses of BAC and performed spirometry to determine the dose-response, reproducibility, and time course of BAC-induced bronchoconstriction.[31] Outcomes evaluated included FEV_1 before and after bronchial challenge as well as the histamine and BAC PD_{20} FEV_1. Bronchoconstriction developed in 25 of 28 subjects (≥10% fall in FEV_1) during BAC inhalation challenge, whereas 17 of 28 had at least a 20% decrease (Fig 2). The dose response to BAC was steep and did not appear to plateau (PD_{20} FEV_1 range 0.35 to 5.5 μmol). There was a significant correlation between histamine PD_{20} FEV_1 and BAC PD_{20} FEV_1 ($r = 0.50$, $P < .05$). Therefore subjects with the greatest inherent airway hyperresponsiveness had the greatest response to BAC. Response to BAC was highly reproducible; there were no significant differences between the mean PD_{20} FEV_1 values in 8 subjects on 2 separate days. Onset of BAC-induced bronchospasm reached a maximum effect on FEV_1 (mean decrease of 28%) within 5 minutes after challenge. Spontaneous recovery from BAC challenge, however, was slow. The majority of FEV_1 values failed to return to 90% of baseline by 60 minutes. The fall in FEV_1 after doubling doses given as aliquots at intervals over time was similar to the fall in FEV_1 after the same total dose (PD_{20}) was given as a single dose. Hence, unlike Na-MBS, the dose of BAC acted cumulatively. This pharmacodynamic property of BAC is likely to be an important factor during repeated dosing of bronchodilators containing BAC, as occurs in the Emergency Department (ED) or Intensive Care Unit (ICU). The mean histamine PD_{20} FEV_1 was 0.18 μmol in 8 subjects 1 hour after BAC challenge compared with a mean of 0.51 μmol ($P < .001$) for histamine challenges performed without BAC pretreatment. Hence, unlike Na-MBS, inhaled BAC enhanced airway responsiveness to histamine because of the longer duration of BAC-induced bronchoconstriction. Response to inhaled BAC was not refractory 60 minutes after a previous BAC challenge. The response to BAC challenge was blocked in 6 subjects pretreated with 4 puffs (8 mg) of nedocromil, but not when pretreated with ipratropium bromide, thus suggesting that BAC has no effect on vagal reflex. It seems likely that BAC acts by release of mast cell mediators.

Unintended bronchoconstriction has been evaluated in commercial solutions containing BAC plus ipratropium and albuterol but not metaproterenol. Strong evidence exists that BAC in combination with EDTA can cause bronchoconstriction in patients with asthma who are given nebulized ipratropium.[28] Ipratropium is now only available as a preservative-free solution; hence the potential problem with this medication and BAC no longer exists. Only one controlled study has examined the effect of BAC on response to albuterol inhalation. Twenty-two patients with mild resting bronchospasm inhaled 2.5 mg of albuterol with and without 50 μg BAC in a blinded fashion.[32] No subject had a fall in FEV_1 greater than 5%. This result is discordant from similar studies conducted with ipratropium and most likely reflects the more potent bronchodilator properties of albuterol. This study sug-

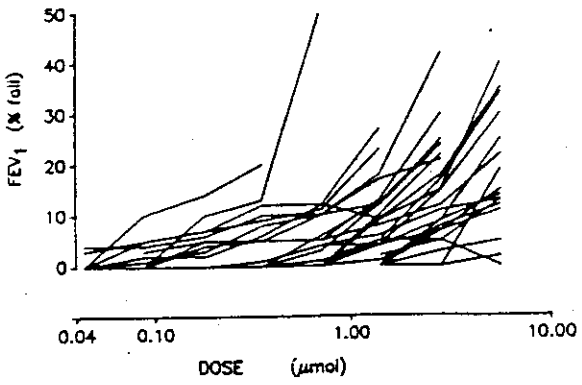

FIG 2. Dose-response to inhaled challenge with benzalkonium chloride in 28 subjects with asthma. Percentage fall from baseline in FEV_1 appears on the ordinate. The cumulative dose of BAC in micromoles appears on the abscissa. One micromole is equivalent to 354 μg of BAC. All but 3 subjects had at least a 10% drop in FEV_1 during BAC challenge; 17 of the 28 subjects had a greater than 20% decrease in FEV_1. (From Zhang YG, Wright WJ, Tarn WK, Nguyen-Dang TH, Salome CM, Woolcock AJ. Effects of inhaled preservatives on asthmatic subjects. II. Benzalkonium Chloride. Am Rev Respir Dis 1990;141:1405-8. Official journal of the American Thoracic Society. © American Lung Association.)

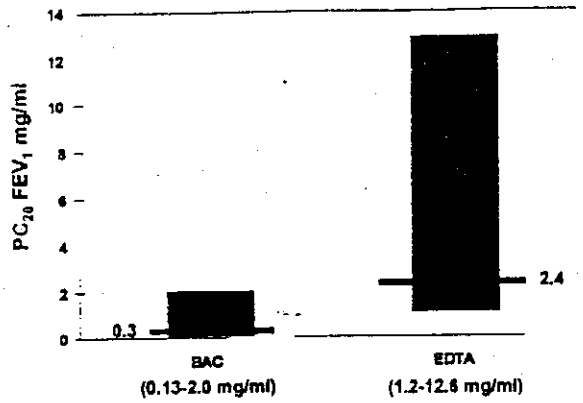

FIG 3. Comparison of the provocational concentration of BAC or EDTA required to induce a 20% decrease from baseline in FEV_1 (PC_{20} FEV_1) in 22 subjects with stable asthma. PC_{20} FEV_1 values (in mg/mL) appear on the ordinate. Bronchoprovocational agent (BAC or EDTA) appears on the abscissa. *Thick horizontal lines* represent mean PC_{20} FEV_1 values for each agent. *Gray bars* represent the range of PC_{20} FEV_1 values for each agent. The ranges are also listed in parenthesis below the agent on the abscissa. (Data from Beasley CRW, Rafferty P, Holgate ST. Bronchoconstrictor properties of preservatives in ipratropium bromide (Atrovent) nebulizer solution. Br Med J 1987;294:1197-8.)

gests that unintended bronchoconstriction is negligible after a single low dose of BAC preserved β_2-agonist in patients with mild bronchospasm. However, the cumulative nature of BAC response on airway patency was not addressed in this study and could have clinically important effects in patients with asthma who are exposed to frequent or continuous nebulized albuterol, especially with the screwcap product that contains 300 μg BAC/2.5 mg albuterol (Table II).

It is extremely important for clinicians to note the great disparity in BAC concentration among nebulized solutions. For example, a 2.5 mg dose of albuterol from a sterile-filled unit-dose vial contains no BAC, a 2.5 mg dose from the unsterile multidose dropper bottle contains 50 μg (approximately 0.2 μmol) BAC, and a 2.5 mg dose from the unsterile screwcap vial contains 300 μg (approximately 1 μmol) of BAC (Fig 1). The BAC PD_{20} FEV_1 occurs over the range 0.35 to 5.5 μmol in patients with asthma.[31] The cumulative nature of the BAC response combined with the fact that the doses of BAC delivered in a single nebulized treatment may be enough to cause significant bronchoconstriction is likely to result in a decreased bronchodilator effect in patients with acute airway obstruction. The problem can be avoided altogether by the use of one of the available preservative-free products.

Chlorobutanol

Chlorobutanol, also known as chlorbutol, is another compound used as a preservative in injectable, ophthalmic, otic, and cosmetic products as well as in several nebulizer solutions (Table I). Chlorobutanol has also been used for a number of years in Europe as an antibacterial preservative in commercially available terbutaline nebulizer solution (Bricanyl, Astra Zeneca, London, U.K.) that is not available in the United States.

Nine atopic patients with asthma underwent bronchial challenge with methacholine (0.13 to 4.0 mg/mL) and chlorobutanol (0.16 to 5.0 mg/mL).[33] Mean methacholine PC_{20} FEV_1 was 0.16 mg/mL (range 0.125 to 0.475 mg/mL). Inhalation of chlorobutanol did not affect lung function in 8 of 9 subjects. One subject had a fall in FEV_1 of greater than 20% after inhalation of 2.5 mg/mL chlorobutanol. The authors conclude that inhalation of up to 5 mg/mL chlorobutanol has no clinically significant effect on airway resistance in patients with stable asthma. Likewise, other investigators demonstrated a lack of effect on lung function in 6 atopic and 2 nonatopic patients with asthma who inhaled a 0.5 mg/mL solution of chlorobutanol.[34]

Although safety has been examined only in a handful of subjects, available data suggest that chlorobutanol does not induce bronchoconstriction over the concentration range of 0.5 to 2.5 mg/mL in subjects with stable asthma. More studies are needed to confirm the safety of this additive in patients with acute bronchospasm, especially when multiple doses of a nebulized solution are administered.

EDTA

The airway effect of EDTA in animal models is well documented. In hypersensitive and nonhypersensitive airway canine models, challenge with EDTA aerosol has been shown to cause important increases in pulmonary resistance as well as a reduction in pulmonary compliance after only 5 minutes.[35,36] The effect of EDTA on airway function lasted at least 25 minutes. The precise mechanism by which chelating agents such as EDTA induce bronchospasm in the canine model is unclear; however, it probably involves mediator release.[37,38] Stimulation of parasympathetic afferent receptors are unlikely to be involved because pretreatment with anti-

cholinergic agents failed to prevent the bronchoconstrictor response to EDTA.[39] However, EDTA-induced bronchospasm is attenuated by albuterol in dogs with hyperreactive airways.[40]

The only study to examine the airway effect of EDTA in patients with asthma was the brief report presented earlier of 6 subjects in whom bronchospasm developed after inhalation of isotonic ipratropium bromide inhalation solution containing 0.25 mg/mL BAC and 0.5 mg/mL EDTA.[28] Subjects received an inhalation challenge with increasing concentrations of EDTA (0.25 to 10.0 mg/mL) in a double-blind fashion. As with BAC, EDTA produced concentration-dependent bronchoconstriction that did not resolve spontaneously within 1 hour. Mean EDTA PC_{20} FEV_1 was 2.4 mg/mL (range 1.2 to 12.8 mg/mL). This compares to mean BAC PC_{20} FEV_1 of 0.3 mg/mL (range 0.13 to 2.0 mg/mL) in the same subjects, suggesting that EDTA is, on average, only one-eighth as potent a bronchoconstrictor as BAC (Fig 3).

Concentrations of EDTA available in nebulizer solutions vary from 0.1 to 0.5 mg/mL. The EDTA PC_{20} FEV_1 range is 1.2 to 12.8 mg/mL (ie, nearly 10-fold greater).[28] The only study to demonstrate paradoxical bronchospasm with EDTA in a commercial product used a relatively weak anticholinergic bronchodilator. Furthermore, the product was preserved with both EDTA and BAC. It is more likely that BAC was responsible for the paradoxical bronchospasm observed in these 6 of 22 subjects with asthma.[28] The effect of EDTA on the bronchodilator response to a solution containing a β_2-agonist and ipratropium (product not available in the United States) has been studied. Eighteen patients with asthma inhaled 0.31 mg/mL fenoterol and 0.13 mg/mL ipratropium bromide with and without 0.5 mg/mL EDTA in a blinded fashion.[41] No significant difference in airway response was observed among treatments. Although these observations are contrary to the bronchoconstriction observed with ipratropium containing EDTA and BAC, it most likely reflects the rapid and potent bronchodilator effect of a β_2-agonist compared with ipratropium. The sum total of information to date on EDTA reassures us that the potential of a single dose of EDTA to cause bronchoconstriction is minimal with the products now available. The potential for bronchoconstriction during multiple dosing is unknown; however, given the near 10-fold difference between the concentrations of EDTA in available commercial products and the PC_{20} FEV_1, it is likely to be of minimal risk unless multiple doses are administered over a short interval (eg, 1 hour, as in the ED treatment of acute airway obstruction).

CONTAMINATION

Contaminated nebulizer solutions have the potential to cause pulmonary infection in susceptible individuals. The aerosol product is introduced directly into the lungs in small (eg, 1 to 5 μm) droplets that partially bypass the natural mucocilliary escalator and cough defense mechanisms. Thus use of contaminated nebulizers or solutions can deliver harmful microorganisms to the lung.

This problem was initially recognized more than 30 years ago in hospitals when large-volume multidose dropper bottles were used to dispense nebulized solutions to several patients.[42-44] Contamination of nebulizer solutions in ambulatory patients is also well documented.[45-47] In most cases, both the nebulizer reservoir and the solution were the most frequent source of contamination. As with inpatients, most contaminated solutions were multidose, large-volume bottles. The most common organisms identified were gram-positive cocci (ie, *Staphylococcus* species) thought to have low pathogenicity.[46] The organisms identified in these studies suggest transfer of organisms from the skin to the nebulizer. In many cases the contaminated products contained BAC, and in one study the multidose dropper with higher BAC concentrations was more often contaminated than unit-dose solutions with lower BAC concentrations.[46] A recent in vitro study indicated that the initial powder of BAC used in manufacturing or extemporaneous compounding by pharmacists is frequently contaminated with microorganisms.[48]

In January 1994, albuterol sulfate inhalation solution in both the multidose dropper bottle and screwcap unit dose vial manufactured by Copley Pharmaceuticals Inc was found to be contaminated with *Pseudomonas fluorescens* bacteria despite the presence of BAC in the formulation.[16] The water supply used to manufacture the solutions was later found to be the contamination source. The FDA negotiated a recall of these products and subsequently received reports of pneumonia in patients in the ICU caused by the same organism isolated from the Copley products. In 1992, another manufacturer recalled its metaproterenol sulfate inhalation solution after the product was found to contain *Burkholderia cepacia*. In 1987, two potential human fungal pathogens (ie, *Aspergillus glaucus* and *Chrysosporium*) were identified in another albuterol sulfate inhalation solution before market distribution.

Clearly, the current manufacturing methods and safeguards against contamination (ie, addition of antimicrobial preservatives), have not prevented microbial contamination of nonsterile inhalation solutions. Furthermore, many species of bacteria are resistant to currently used preservative agents, and use of a single preservative in the manufacture of a nonsterile inhalation solution for an extended period could actually select for preservative-resistant strains. These contamination problems, along with adverse experience reports, have led the FDA to propose a sterility requirement for all aqueous-based inhalation solutions for nebulization.[16] While this proposed rule change is a step in the right direction, the proposal is less than ideal because it does not mandate the removal of preservatives or the use of unit-dose packaging. This proposed FDA rule has not yet been finalized. When approved, all manufacturers of nonsterile solutions for inhalation will have 1 year after the publication of the final rule to comply with sterility requirements.[16]

RECOMMENDATIONS

The less β_2-selective adrenergic agonists (eg, iso-

etharine) and nonselective adrenergic bronchodilators (eg, isoproterenol) should not be used in any clinical situation. They contain enough sulfite in each dose to cause unintended bronchospasm, which could decrease the efficacy of the bronchodilator or produce paradoxical worsening of acute airway obstruction. Even though they may be less expensive than newer agents, the risks clearly outweigh any economic considerations. Racemic epinephrine should not be used to treat upper airway obstruction in an infant with coexisting reactive airway disease. In such patients, epinephrine from the preservative-free intravenous ampule should be used in place of racemic epinephrine.

Albuterol, the most commonly prescribed nebulized bronchodilator, is often administered without knowledge or concern of the effects of additives. Some solutions contain additives, but some do not. Most sterile-filled unit-dose solutions are additive free and would be appropriate to use in all clinical situations. One of these sterile-filled products (manufactured by Dey Laboratories) contains 300 μg EDTA in each 2.5 mg dose. This amount of EDTA is one-tenth the concentration known to induce bronchoconstriction. Despite the fact that we know little about the cumulative nature of the response to EDTA, it seems likely that this product is safe to use when a single dose is administered at intervals of 2 hours or more. All nonsterile nebulized albuterol formulations contain BAC. The multidose dropper bottle contains 50 μg (approximately 0.2 μmol) BAC in each 2.5 mg albuterol dose. Because this amount of BAC is less than the threshold dose for bronchoconstriction during a single administration,[31] this product is also acceptable as long as a single dose is administered at intervals of 2 hours or longer. However, National Institutes of Health (NIH) guidelines for the treatment of asthma exacerbations in the ED recommend 2.5 to 5 mg of nebulized albuterol every 20 minutes for 3 doses, then 2.5 to 10 mg every 1 to 4 hours as needed.[49] For the multidose dropper bottle, this translates into 300 μg BAC (approximately 1 μmol) during the first hour. The BAC PD_{20} FEV_1 occurs over the range 0.35 to 5.5 μmol,[31] hence some patients with acute asthma treated with nebulized albuterol from a multidose dropper bottle in the ED would receive enough BAC to cause significant bronchoconstriction. The multidose dropper bottle form of nebulized albuterol is, therefore, not appropriate for use in the ED. The nonsterile, unit-dose, screw-cap, albuterol nebulizer solution contains 300 μg (approximately 1 μmol) BAC in each 2.5 mg dose. This product has enough BAC in a single dose to cause significant bronchoconstriction and should not be used for acute therapy. In the ED, for example, if the NIH guidelines are followed, this product will deliver as much as 1800 μg of BAC in the first hour.

Ipratropium, another commonly prescribed bronchodilator, is manufactured as a sterile-filled unit-dose solution that contains no bronchoconstrictor additives. Levalbuterol is now available as sterile-filled, unit-dose, additive-free vials for nebulization.

Because antibacterial additives may not prevent bacterial contamination of nebulized solutions, and it is irrational to give a bronchoconstrictor to patients with bronchospasm, we recommend that only additive-free sterile-filled unit-dose bronchodilator solutions be used with a nebulizer to treat acute airway obstruction when doses are required hourly or continuously, as in the ED or ICU.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-664

ADMINISTRATIVE DOCUMENTS

Printed by Gregory Davis

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 11-Nov-1999 02:18pm
From: Doug Sporn
SPORND
Dept: HFD-600 MPN2 286
Tel No: 301-827-5845 FAX 301-594-0183

TO: See Below
Subject: Re: nephron

Bob,

Gary apparently did not see your message before he left work yesterday. With respect to your question about Alpharma, we have not heard a word from them since the NA letter issued. I suspect that, for what ever reason, they may have lost interest in the product. If the past they have not been shy about contacting us when ever they wanted to pursue an ANDA approval.

In the case of Nephron, you are welcome to take some more time to think about any remaining safety concerns and discuss these with your staff or Dr. Jenkins before reaching a final conclusion. Eventually we will need a brief memo from you stating unequivocally that either a) you believe the product is sufficiently safe to be submitted as an ANDA or b) it isn't safe based on the information you have to make that determination.

I apologize if this sounds like I am trying to put you on the spot. It is just that I have seen enough similar situations to believe that without that kind of clarity we could possibly have bigger problems down the road with scientific and legal challenges to this being a j product from other firms.

If you would like my staff to prepare a draft of the type of memo we need for you to consider, please let me know. We would be happy to do it.

Thanks,

Doug

Gary,

I think some of our concerns are theoretic and therefore could not be addressed given the substitutability paradigm. I am not trying to be evasive, but this issue raises some concerns which I believe were shared by Dr. Hendeles (to Nephron's chargin), but our regulatory realities are what they are. I would say that you folks should go ahead with your

best judgement. We would be happy to provide some input on the adequacy of labeling if you feel that would be helpful. What is going to happen with Alpharma's NA action?

Bob

Distribution:

TO: Robert Meyer		(MEYERRO)
TO: Gary Buehler		(BUEHLER)
TO: John Grace		(GRACEJ)
TO: Gregory Davis		(DAVISG)
TO: Parinda Jani		(JANIP)
TO: Jim Morrison		(MORRISONJ)
TO: Gregory Davis		(DAVISG)
TO: Cecelia Parise		(PARISEC)
TO: William Rickman		(RICKMAN)
TO: Michael Smela		(SMELA)
TO: KIM E DETTELBACH	(OC)	(KDETTELB@OC.FDA.GOV)
TO: Guiragos Poochikian		(POOCHIKIAN)
TO: Frank Holcombe		(HOLCOMBE)
TO: Donald Hare		(HARE)
TO: Nasser Mahmud		(MAHMUDN)
TO: Paras Patel		(PATELP)
TO: Eugene Sullivan		(SULLIVANEU)
TO: Badrul Chowdhury		(CHOWDHURYB)
TO: Vibhakar J. Shah		(SHAHVJ)

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Phone: 407-246-1389
Fax: 407-872-0001

Nephron Pharmaceuticals Corp.

Fax

To:	Mr. John Grace, Div. Labeling Spt.	**From:**	Steven F. Simmons
Fax:	301.443.3847	**Date:**	November 4, 1999
Phone:	301.827.5846	**Pages:**	2
Re:	Labeling Proposal	**CC:**	Mr. Greg Davis, FAX 301.594.1174

☐ **Urgent** ☑ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

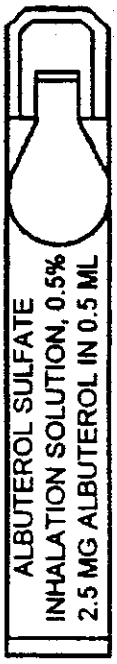
•Comments:

Mr. Grace,

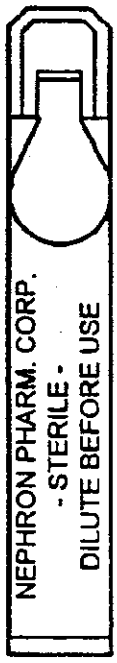
This is a follow-up to our meeting on November 3, 1999. I am sending the attached labeling diagrams per David Rosen. Please look over the attached proposed labeling for a single 0.5 mL vial of 0.5% albuterol sulfate inhalation solution and provide us with your comments concerning this type of labeling for an ANDA or NDA product.

Sincerely,

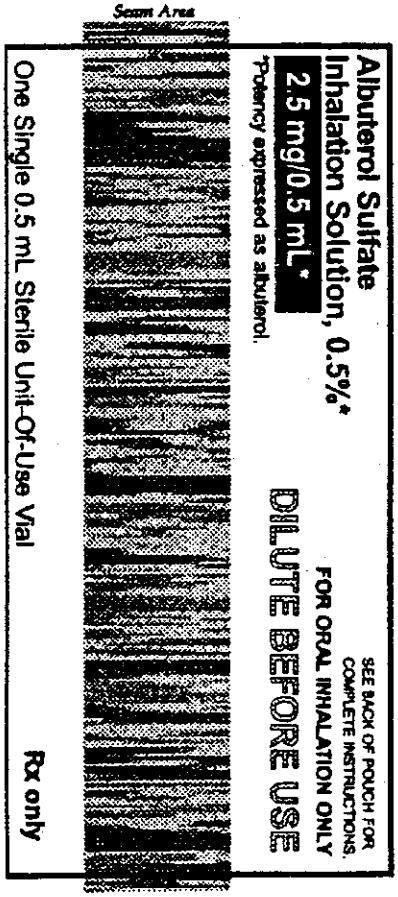
Steven F. Simmons



FRONT



BACK



Patient's Instructions For Use

Read complete instructions carefully before using.

1. Twist open the top of one albuterol sulfate inhalation solution unit-of-use container (Figure 1).
2. Squeeze the solution into the nebulizer reservoir through the appropriate opening (Figure 2).
3. Add 2.5 mL of sterile normal saline solution, as your doctor has directed.
4. Gently swirl the nebulizer to mix the contents and connect it with the mouthpiece or face mask (Figure 3).
5. Connect the nebulizer to the compressor.
6. Sit in a comfortable, upright position; place the mouthpiece in your mouth (Figure 4) (or put on the face mask); and turn on the compressor.
7. **Breathe as calmly, deeply, and evenly as possible until no more mist is formed in the nebulizer chamber (about 5 to 15 minutes). At this point, the treatment is finished.**
8. Clean the nebulizer (see manufacturer's instructions).

Please consult your doctor before use. Do not exceed recommended dose.

Figure 1

Figure 2

Figure 3

Figure 4

nephron pharmaceuticals corporation
Orlando, FL 32811

rev. 11-04-99

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Final

Meeting Minutes

ANDA # and Drug Name:	75-664, Albuterol Sulfate Inhalation Solution, 0.5%
Meeting Date:	November 3, 1999
Time:	4:30 – 5:30 PM
Location:	Conference Room B, MetroPark North II
Indication:	Relief of bronchospasm
Sponsor:	Nephron Pharmaceuticals Corp.
Type of Meeting:	Informal Conference in response to Refuse to File Letter
Meeting Facilitators:	Gary Buehler and Gregory S. Davis
Sponsor Participant Lead:	Steve Simmons
Project Manager:	Gregory S. Davis
FDA Participants:	Robert Meyer, M.D., Division of Pulmonary and Allergy Drug Products Parinda Jani, Division of Pulmonary and Allergy Drug Products Guirag Poochikian, Office of New Drug Chemistry Gary Buehler, Office of Generic Drugs John Grace, Office of Generic Drugs Mike Smela, Office of Generic Drugs Don Hare, Office of Generic Drugs Gregg Davis, Office of Generic Drugs Paras Patel, Office of Generic Drugs Kim Dettelbach, Office of Chief Counsel Jim Morrison, Ombudsman
Sponsor Participants:	Steven S. Simmons, President, Nephron J. Brian Lundberg, Director, Quality Assurance, Nephron Leslie Hendeles, Pharm. D., Univ. of Florida, College of Pharmacy David Rosen, J.D., McDermott, Will & Emery

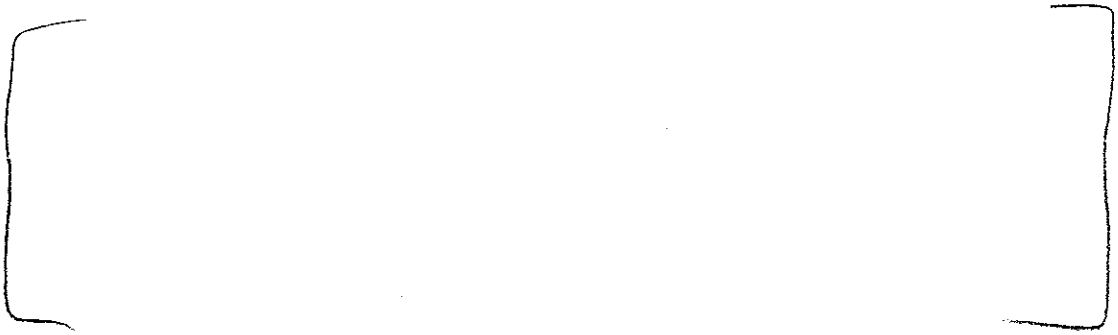
Meeting Objective:

To discuss the safety issues raised By the Division of Pulmonary and Allergy Drug Products and the Office of Generic Drugs regarding the submission of an abbreviated new drug application (ANDA) for a concentrated albuterol sulfate inhalation solution, 0.5%, packaged in a unit-of-use configuration.

Background:

Albuterol Sulfate Inhalation Solution is a relatively selective beta$_2$–adrenergic bronchodilator used clinically for the relief of bronchospasm in patients 2 years of age and older with reversible obstructive airway disease and acute attacks of bronchospasm. Nephron submitted an ANDA; 75-664, for Albuterol Sulfate Inhalation Solution, 0.5% on July 2, 1999, received by the Agency on July 6, 1999. After a regulatory review of this application for acceptability and completeness of filing, it was determined that this application was deficient and required the following issues addressed before it could be considered substantially complete for review:

1. The Division of Pulmonary and Allergy Drug Products (DPADP) and the Office of Generic Drugs had determined that there were safety concerns regarding a concentrated product (0.5%) that is packaged for single use but requires further dilution.



As stated in the Agency's Refuse to File letter dated August 13, 1999, the applicant may amend the application to include the above listed information or request in writing an informal conference to discuss the issues raised in the letter. The applicant has 30 days from the date of the Refuse to File letter to amend the application or request the conference.

On September 7, 1999, the Agency received a letter from Nephron Pharmaceuticals requesting an informal conference. On September 8, 1999, the Agency received a response from Nephron adequately addressing the last four issues and providing an additional copy of the informal conference request. This request for conference was administratively converted to a control document, #99-347. The conference was then scheduled for November 3, 1999.

It is Nephron's belief that the proposed product in the proposed container provides benefits to the public and does not raise safety concerns. The benefits are as follows:

1. The proposed product is a sterile drug product as opposed to the non-sterile multi-dose containers currently on the market for this product.

2. The proposed product is free of preservatives (known to cause potential allergic reactions which may pose a danger to patients with pulmonary disorders.

3. The proposed product unit-of-use dispensing provides additional assurance against microbial contamination as opposed to the non-sterile drug products, which have increased bioburden with each successive entry of the bottle by the dropper.

Agenda Item 1: Introduction and a review of the currently FDA-approved multi-dose drug products

Unresolved Issues:
None.

Action Items:
None.

Agenda Item 2: Discussion of safety concerns for multi-dose versus unit-of-use containers for concentrated solutions

Agreements:
OGD and the Division agree with the sponsor that a preservative-free inhalation solution may protect public health by decreasing potential adverse events associated with preservative- induced bronchospasm.

Unresolved Issues:

Agenda Item 3: Clinicians perspective on possible safety issues

The following issues were addressed:

- Physicians counsel patient/caregiver on the proper technique for using nebulized products
- Pharmacists counsel patient/caregiver on the proper technique for using nebulized products
- Written patient instructions are provided with the product at the time of dispensing noting product must be diluted prior to use

- Instructions are also on the product itself

- It is standard clinical practice to demonstrate the appropriate dosage and administration for nebulized products prior to dispensing

Agreements:
The Division and OGD agree with all points raised except for the fourth issue, as listed above. The Agency disagrees that the instructions are on the product itself and has concerns that if the overwrap is discarded, the patient instructions will be discarded as well.

Unresolved Issues:
The Agency believes that the most appropriate route for submission of this product would be a 505(b)(2) application as this route would allow for the differences in labeling to assure patient safety and the correct use and administration. However, the Agency will entertain the re-submission of this product as a 505(j) application if the sponsor manufactures another batch and packages the product individually with individual labeling.

Action Items:
The sponsor will either withdraw their application and re-submit the information to the Division as a 505(b)(2) application or manufacture another batch, package the nebules individually and amend their 505(j) application.

Prepared by: /S/
Gregory S. Davis, Project Manager

Date: 2/24/00

Concurrence: /S/
Gary Buehler, Dept Director, OGD

Date: 2/24/00

2/9/00 Hearing minutes

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Page(s) of trade secret and /or confidential commercial information

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: ANDA 75664/000
Stamp: 06-JUL-1999
Regulatory Due:
Applicant: NEPHRON
4121 SOUTHWEST 34TH ST
ORLANDO, FL 328116458
Priority:
Org Code: 600

Action Goal:
District Goal: 06-JUN-2000
Brand Name:
Estab. Name: ALBUTEROL SULFATE
Generic Name:
Dosage Form: (SOLUTION)
Strength: 0.5%

Application Comment: THIS PRODUCT IS A SOLUTION FOR INHALATION (on 02-MAR-2000 by G. DAVIS (HFD-615) 301-827-5862)

FDA Contacts: M. DILLAHUNT (HFD-613) 301-827-5848 , Project Manager
M. SMELA JR (HFD-625) 301-827-5848 , Team Leader

Overall Recommendation:
Establishment: [redacted]

DMF No: [redacted] AADA:
Responsibilities: [redacted]
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	02-MAR-2000				DAVISG

Establishment: [redacted]

DMF No: AADA:
Responsibilities: [redacted]
Profile: CTL OAI Status: NONE
Estab. Comment: THIS SITE WILL DO [redacted] (on 02-MAR-2000 by G. DAVIS (HFD-615) 301-827-5862)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	02-MAR-2000				DAVISG

Establishment: 1054871
NEPHRON PHARMACEUTICALS CORP
4121 SOUTHWEST 34TH ST
ORLANDO, FL 328116458
DMF No: AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
Profile: LIQ OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	02-MAR-2000				DAVISG

Establishment: [redacted]

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

DMF No: AADA:
Responsibilities:
Profile: CTL OAI Status: NONE
Estab. Comment: THIS SITE WILL DO 02-MAR-2000 by G. DAVIS (HFD-615) 301-827-5862)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	02-MAR-2000				DAVISG

APPEARS THIS WAY ON ORIGINAL

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

ANDA Number: 75-664

Date of Submission: February 16, 2000

Applicant's Name: Nephron Pharmaceuticals Corporation

Established Name: Albuterol Sulfate Sterile Solution for Inhalation by Nebulizer, 0.5% (2.5 mg/0.5 mL)

Labeling Deficiencies:

1. CONTAINER – Unit-of-Use Plastic Vial (0.5 mL)

   Satisfactory in **draft**

2. CARTON – Box of 30 Unit-of Use Vials

   Back Panel:
   a. Patient Instructions For Use-

      Include the entire directions for step # 6 on your labels.

3. FOIL POUCH

   See comment 2.(b.) under CARTON above.

4. INSERT:

   a. General Comments:

      Due to changes in the approved labeling of the reference listed drug;[Proventil Solution for Inhalation 0.5%; approved March 13, 2000] revise your package insert labeling accordingly.
      (Please refer to the enclosed March 13, 2000 approval letter and labeling.)

   b. PATIENTS INSTRUCTIONS FOR USE section:

      i. First sentence: revise to read as follows:

         Note: The Albuterol Sulfate Inhalation Solution is concentrated and must be...

      ii. Comment # 8: Revise to include the following -

         ...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.

iii. Replace the statement [redacted] with the following:

Mixing Compatibility: The safety and effectiveness of Albuterol sulfate solution for inhalation have not been determined when one or more drugs are mixed with it in a nebulizer. [redacted]

Please revise your labels and labeling, as instructed above, and submit in final print or draft if you prefer.

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

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

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

ENCLOSURE: A copy of the most recently approved labeling of the reference listed drug; Proventil Inhalation Solution, 0.5%; approved March 13, 2000.

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's 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 24**		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			
PROPRIETARY NAME			
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 -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR. **(Individual 2.5 mg/0.5mL unit-of-use containers packaged in cartons of 30 for concentrated albuterol 0.5%)**	x		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC, [see FTR]		X	
Does the package proposed have any safety and/or regulatory concerns? **There were some concerns however, after meetings between Nephron Pharmaceutical and OGD they have** been resolved.		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	
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 (p. #) 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 p. # 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 bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD:

1. Review was NOT based on the labeling of the most recently approved labeling for the reference listed drug ;Proventil Solution for Inhalation 0.5%; approved March 13, 2000; 19-243/S-014. We will send a copy of this insert for the firm to utilize.

2. Patent/ Exclusivities:
   The patent that exist for this drug product has expired. The firm is filing paragraph II (see section 3.1 in volume A.2.1.)

3. Storage/Dispensing Conditions:
   NDA: Store between 2° - 25°C(36° - 77°F).

   ANDA: Same as RLD

4. Product Line:
   The innovator markets their 0.5% strength Albuterol Solution for Inhalation product in 20 mL glass amber bottles containing a calibrated dropper.

   The applicant proposes to market their product in plastic, sterile unit-of-use vials of 0.5 mL (2.5 mg/0.5mL) individually packed in a foil package available in cartons of 30 units.

5. Inactive Ingredients:
   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 148 Vol. 1.1.

6. **Note that the firm relocated the statements "DILUTE BEFORE USE" and " FOR ORAL INHALATION ONLY" to the front panel of the CARTON and is on the front panel of the POUCH. I feel that this was a good idea to alleviate some safety concerns.**

   Also Note that the firm did NOT include the paragraph '

Date of Review: 7/12/00 Date of Submission: 2/16/00

Primary Reviewer: Jim Barlow /S/ Date: 8/18/00

Team Leader: John Grace /S/ Date: 8/18/2000

cc:

ANDA: 75-664
DUP/DIVISION FILE
HFD-613/JBarlow/JGrace (no cc)
V:\FIRMSNZ\NEPHRON\LTRS&REV\75664NA1.L
Review

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **ANDA 75664/000**
Stamp: **06-JUL-1999** Regulatory Due:
Applicant: **NEPHRON**
4121 SOUTHWEST 34TH ST
ORLANDO, FL 328116458

Priority:
Action Goal:
Brand Name:
Established Name: **ALBUTEROL SULFATE**
Generic Name:
Dosage Form: **SOL (SOLUTION)**
Strength: **0.5%**

Org Code: **600**
District Goal: **06-JUN-2000**

FDA Contacts: **M. DILLAHUNT (HFD-613) 301-827-5848 , Project Manager**
M. SMELA JR (HFD-625) 301-827-5848 , Team Leader

Overall Recommendation:

Establishment: [redacted]
DMF No: [redacted]
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **02-MAR-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: [redacted]

Establishment: [redacted]
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **02-MAR-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: [redacted]

Establishment: **1054871**
NEPHRON PHARMACEUTICALS COI
4121 SOUTHWEST 34TH ST
ORLANDO, FL 328116458
DMF No:
AADA No:

Profile: **LIQ** OAI Status: **NONE**
Last Milestone: **ASSIGNED INSPECTION TO IB**
Milestone Date: **30-JUN-2000**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Establishment: [redacted]

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **02-MAR-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: [redacted]

APPEARS THIS WAY
ON ORIGINAL

file : ANDA 75-664

Memorandum of Telephone Conference
February 14, 2001

Representing Nephron Pharmaceuticals:

Steven F. Simmons, President
J. Brian Lundberg, Director, QA
David Rosen, R. Ph., J.D. McDermott, Will & Emery

FDA Participants:

Gary Buehler, Acting Director, OGD
Andrea High, Ph.D., Team Leader, Microbiology
Rita Hassall, OGD

Purpose:

The conference was held in lieu of a meeting as requested by the firm in a letter dated January 12, 2001 (Control 01-026). The request was to discuss microbiology deficiencies identified in the ANDA 75-664, Albuterol Sulfate Inhalation Solution, 0.5%.

Note: The firm had planned to have a [redacted] participate in the meeting. It was pointed out that [redacted] had been a reviewer of another, related Nephron application referenced in their communication when he was with the agency. Because of this, it was requested he not participate in the conference. The firm and [redacted] readily complied with the request.

Discussion:

Mr. Simmons began the discussion with a summary of the application and the deficiencies identified. He noted changes that had been made in their process based on findings related to an application for another product. They requested the agency's view point on the current situation.

Dr. High provided the following responses to the firm:

- The current expectations for inhalation solutions applications are different than they [redacted]
- [redacted]

- It is important that the firm understand the sterility assurance expectations for applications currently under review or to be submitted. In addition, at the time the final rule on the sterility of inhalation solutions goes into effect, approved applications will have to have validated methods to demonstrate the firm can manufacture sterile products.
- Each product must stand on its own. Therefore, data from other products may not be considered in applications for different products. Processes can't be assumed to carry over through all product lines. The validation may be applied to other concentrations of the same products, however.

The firm will submit a protocol for the challenge test and will fully respond to the minor amendment.

/S/
Rita R. Hassall

q:\firms-nz\nephron\01-026

Drafted: R. Hassall 2/14/01
Edited per A. High 2/14/01
Concur: G. Buehler 2/15/01

cc: ANDA 75-664
A. High

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

ANDA Number:	75-664
Date of Submission:	March 29, 2001
Applicant's Name:	Nephron Pharmaceuticals Corporation
Established Name:	Albuterol Sulfate Sterile Solution for Inhalation by Nebulizer, 0.5% (2.5 mg/0.5 mL)

Labeling Deficiencies:

1. CONTAINER – Unit-of-Use Plastic Vial (0.5 mL)
   Satisfactory in **draft** as of the February 16, 2000 submission

2. CARTON – Box of 30 Unit-of Use Vials
   Satisfactory in **draft** as of the March 29, 2001 submission

3. FOIL POUCH
   Satisfactory in **draft** as of the March 29, 2001 submission

4. INSERT:
   PATIENTS INSTRUCTIONS FOR USE section:

   Replace the statement '[redacted].' with the following:

   Mixing Compatibility: The safety and effectiveness of Albuterol sulfate solution for inhalation 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.

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

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/

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

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's 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 24**		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			
PROPRIETARY NAME			
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 -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR. **(Individual 2.5 mg/0.5mL unit-of-use containers packaged in cartons of 30 for concentrated albuterol 0.5%)**	x		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. [see FTR]		X	
Does the package proposed have any safety and/or regulatory concerns? **There were some concerns however, after meetings between Nephron Pharmaceutical and OGD they have** been resolved.		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	
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 (p. #) 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 p. # 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 bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD:

1. **Review was based on the labeling of the most recently approved labeling for the reference listed drug ;Proventil Solution for Inhalation 0.5%; approved March 13, 2000; 19-243/S-014.**

2. Patent/ Exclusivities:
   The patent that exist for this drug product has expired. The firm is filing paragraph II (see section 3.1 in volume A.2.1.)

3. Storage/Dispensing Conditions:
   NDA: Store between 2° - 25°C(36° - 77°F).

   ANDA: Same as RLD

4. Product Line:
   The innovator markets their 0.5% strength Albuterol Solution for Inhalation product in 20 mL glass amber bottles containing a calibrated dropper.

   The applicant proposes to market their product in plastic, sterile unit-of-use vials of 0.5 mL (2.5 mg/0.5mL) individually packed in a foil package available in cartons of 30 units.

5. Inactive Ingredients:
   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 148 Vol. 1.1.

6. **Note that the firm relocated the statements "DILUTE BEFORE USE" and " FOR ORAL INHALATION ONLY" to the front panel of the CARTON and is on the front panel of the POUCH. I feel that this was a good idea to alleviate some safety concerns.**

   Also Note that the firm did NOT include the paragraph '

Date of Review: 4/13/01 Date of Submission: 3/29/01

Primary Reviewer: Jim Barlow Date: 4/13/01

Team Leader: John Grace Date: 4/17/2001

-/S/

cc:

ANDA: 75-664
DUP/DIVISION FILE
HFD-613/JBarlow/JGrace (no cc)
V:\FIRMSNZ\NEPHRON\LTRS&REV\75664na2.I
Review

File 75664

FAX

nephron pharmaceuticals corporation
4121 SW 34th Street, Orlando, Florida, 32811

Date April 17, 2001
Number of pages including cover sheet 9

To:	From:
Shirley Brown	Brian Lundberg
FDA	Steve Simmons
Phone	Phone 407-246-1389
Fax Phone (301) 594-1040	Fax Phone 407-872-0001
0180	

REMARKS:

☐ Urgent ☐ For your review ☐ Reply ASAP ☐ Please comment

Telephonic Amendment

ANDA 75-664

Hard Copy mailed Airborne Express. will arrive 4-18-01 (S.F.S.)

Steve, Ready to fax in the morning

4. NUMBER OF VOLUMES SUBMITTED: 1 Archive Copy, containing 1 volumes
   1 Review Copy, containing 1 volumes
   1 Field Submission Copy, containing 1 volumes, (submitted to the Orlando District)

5. THIRD COPY CERTIFICATION STATEMENT: We certify that the third (field) copy of this Abbreviated New Drug Application contains a true copy of all sections, both administrative and technical and has been sent directly to the Orlando District Office.

6. Rx / OTC DRUG STATEMENT: This application is for the production of a prescription drug product (Rx).

7. FACILITY PERSONNEL: The following Nephron Pharmaceuticals Corporation personnel are available to answer questions concerning this submission:

Administration:	Steven F. Simmons, President
Quality Assurance:	J. Brian Lundberg, Director of Quality Assurance
Quality Control:	Angel Pérez, Manager - Quality Control, Chemistry
	Karen Pendleton, Manager - Quality Control, Microbiology
Production:	Raúl Lugo, Manager - Production

8. CONSULTANTS: The following consultants are authorized to act on behalf of Nephron Pharmaceuticals Corporation concerning this ANDA, in the following capacities:

Outside Counsel: David L. Rosen, R.Ph., J.D.
Attorney at Law
McDermott, Will & Emery
600 13th St, N.W.
Washington, DC 20005-3096
(202) 756-8075

[redacted]

[redacted]

We appreciate the agency's expedient review of our application, and look forward to an early reply.

Sincerely,

NEPHRON PHARMACEUTICALS CORP.

Steven F. Simmons
President

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page

FOR FDA USE ONLY

APPLICATION NUMBER
75-664

APPLICATION INFORMATION

NAME OF APPLICANT
Nephron Pharmaceuticals Corporation

DATE OF SUBMISSION
APR 17 2001

TELEPHONE NO *(Include Area Code)*
(407) 246-1389

FACSIMILE (FAX) Number *(Include Area Code)*
(407) 872-0001

APPLICANT ADDRESS *(Number, Street, City, State and Zip Code or Mail Code)*:
4121 34th Street
Orlando, FL 32811-6458

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, State, and Zip Code telephone & FAX number) IF APPLICABLE*

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)

ESTABLISHED NAME *(e.g. Proper name, USP/USAN name)*
Albuterol Sulfate

PROPRIETARY NAME *(trade name)* IF ANY

CHEMICAL / BIOCHEMICAL NAME *(If any)*

CODE NAME *(If any)*
α^1-[(tert-Butylamino)methyl]-4-hydroxy-m-xylene-α-α'-diol sulfate (2:1) (salt)

DOSAGE FORM
Sterile Solution for Inhalation by Nebulizer

STRENGTHS
0.5% (2.5 mg/0.5 mL)

ROUTE OF ADMINISTRATION
Inhalation

PROPOSED INDICATIONS FOR USE
For relief of bronchospasm in patients with reversible obstructive airway disease and acute attacks of bronchospasm.

APPLICATION INFORMATION

APPLICATION TYPE *(Check one)*
☐ NEW DRUG APPLICATION (21 CFR 314.50) ☒ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGIC APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug	Holder of Approved Application
Ventolin (albuterol sulfate USP) inhalation solution 0.5%	**Glaxo Corporation**

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☒ AN AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ NOTIFICATION ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT
☐ SUPAC SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT

REASON FOR SUBMISSION
Telephonic Amendment for Chemistry Review

PROPOSED MARKETING STATUS *(Check One)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Refer to attached sheet for complete listing

Cross References (list related License Application, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA 19-269 Glaxo Inc. DMF ANDA
DMF DMF

FORM FDA 356h (4/97)

This application contains the following items: *(Check all that apply)*			
	1. Index		
	2. Labeling (check one)	☐ Draft Labeling	☐ Final Printed Labeling
	3. Summary (21 CFR 314.50(c))		
	4. Chemistry Section		
	a. Chemistry, manufacturing, and control information (e.g. 21 CFR 314.50(d)(1))		
	b. Samples (21 CFR 314.50 (e)(1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)		
	c Methods Validation Package (21 CFR 314.50(e)(2)(i))		
	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50(d)(2))		
	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50(d)(3)) .		
	7. Clinical Microbiology (21 CFR 314.50(d)(4))		
	8. Clinical data section (21 CFR 314.50(d)(5))		
	9. Safety update report (21 CFR 314.50 (d)(5)(vi)(b))		
	10. Statistical section (21 CFR 314.50(d)(6))		
	11. Case report tabulations (21 CFR 314.50(f)(1))		
	12. Case reports forms (21 CFR 314.50(f)(1))		
	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))		
	14 A patent certification with respect to any patent which claims the drug (21 U.S.C. 355(b)(2) or (j)(2)(A))		
	15. Establishment description (21 CFR Part 600, if applicable)		
	16. Debarment certification		
x	17 Field copy certification		
	18. User Fee Cover Sheet (Form FDA 3397)		
x	19. OTHER *(Specify)* **Telephonic Amendment per Chemistry**		

CERTIFICATION

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610 and/or 809.
4. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80 and 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the drug enforcement administration makes a final scheduling decision.

The data and information in this submission have been reviewed and are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Steven F. Simmons President	APR 17 2001

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to , a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address

FORM FDA 356h (4/97)

Redacted 1

pages of trade secret and /or confidential commercial information

REFERENCE: Telephonic Amendment Items

1. Attached, please find a copy of the revised In-Process Product Specification Form and Finished Product Specification Form for the proposed drug product. The specification forms have been modified to include the qualitative identification test for ——— as requested. The test will be that specified in USP <191> ———
2. Nephron confirms that the foil film identified as ———nanufactured by ———————————, will be used as a ——————— or the proposed drug product.

APPEARS THIS WAY ON ORIGINAL

In process Specification form

Redacted 2

pages of trade secret and/or confidential commercial information

File

RECORD OF TELEPHONE CONVERSATION

Information for two issues were requested.

1. Revise the drug product release specifications to include testing for [redacted]" per USP <191>.

2. Confirm that the drug product foil pouch material used for commercial batches is [redacted]

The applicant agreed to provide the information by a telephone amendment with a copy to Shirley Brown's attention.

APPEARS THIS WAY ON ORIGINAL

DATE 4/17/01

ANDA NUMBER
75-664

IND NUMBER

TELECON

INITIATED BY

SPONSOR

X FDA

PRODUCT NAME

Albuterol Sulfate Inhalation Solution, 0.5%

FIRM NAME

Nephron Pharmaceutical Corp.

NAME AND TITLE OF PERSONS WITH WHOM CONVERSATION WAS HELD

Steven Simmons, President

Brian Lundberg, QA Director

TELEPHONE NUMBER

(407) 246-1389

SIGNATURES

/S/

Smela Jr, Michael

From: Smela Jr, Michael
nt: Tuesday, April 24, 2001 11:16 AM
: Dillahunt, Michelle
Cc: Brown, Shirley S
Subject: 75664

I am closing this. Micro and Labeling reviews are pending. Please add to approval matrix.

Mike

APPEARS THIS WAY
ON ORIGINAL

5.1

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

ANDA Number:	75-664
Date of Submission:	April 30, 2001
Applicant's Name:	Nephron Pharmaceuticals Corporation
Established Name:	Albuterol Sulfate Sterile Solution for Inhalation by Nebulizer, 0.5% (2.5 mg/0.5 mL)

Labeling Deficiencies:

1. CONTAINER – Unit-of-Use Plastic Vial (0.5 mL)
   Satisfactory in **draft** as of the February 16, 2000 submission

2. CARTON – Box of 30 Unit-of Use Vials
   Satisfactory in **draft** as of the March 29, 2001 submission

3. FOIL POUCH
   Satisfactory in **final print** as of the April 30, 2001 submission

4. INSERT:
   Satisfactory in **final print** as of the April 30, 2001 submission

Please prepare and submit **12 copies of final print** for your CONTAINER and CARTON labels.

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

/S/

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

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's 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 24**		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			
PROPRIETARY NAME			
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 -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR. **(Individual 2.5 mg/0.5mL unit-of-use containers packaged in cartons of 30 for concentrated albuterol 0.5%)**	x		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. [see FTR]		X	
Does the package proposed have any safety and/or regulatory concerns? **There were some concerns however, after meetings between Nephron Pharmaceutical and OGD they have** been resolved.		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	
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 (p. #) 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 p. # 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 bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD:

1. **Review was based on the labeling of the most recently approved labeling for the reference listed drug ;Proventil Solution for Inhalation 0.5%; approved March 13, 2000; 19-243/S-014. As of the April 30, 2001 submission, the firm submitted final printed FOIL POUCH labeling and final printed INSERT labeling.**
2. Patent/ Exclusivities:
   The patent that exist for this drug product has expired. The firm is filing paragraph II (see section 3.1 in volume A.2.1.)
3. Storage/Dispensing Conditions:
   NDA: Store between 2° - 25°C(36° - 77°F).
   ANDA: Same as RLD
4. Product Line:
   The innovator markets their 0.5% strength Albuterol Solution for Inhalation product in 20 mL glass

amber bottles containing a calibrated dropper.

The applicant proposes to market their product in plastic, sterile unit-of-use vials of 0.5 mL (2.5 mg/0.5mL) individually packed in a foil package available in cartons of 30 units.

5. Inactive Ingredients:
   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 148 Vol. 1.1.
6. **Note that the firm relocated the statements "DILUTE BEFORE USE" and " FOR ORAL INHALATION ONLY" to the front panel of the CARTON and is on the front panel of the POUCH. I feel that this was a good idea to alleviate some safety concerns.**
   Also Note that the firm did NOT include the paragraph " _____

Date of Review: 5/22/01 Date of Submission: 4/30/01

Primary Reviewer: Jim Barlow Date: 5/25/01

Team Leader: John Grace Date: 6/6/2001

cc:

ANDA: 75-664
DUP/DIVISION FILE
HFD-613/JBarlow/JGrace (no cc)
V:\FIRMSNZ\NEPHRON\LTRS&REV\75664na3.l
Review

APPEARS THIS WAY
ON ORIGINAL

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

ANDA Number:	75-664
Date of Submission:	April 30, 2001
Applicant's Name:	Nephron Pharmaceuticals Corporation
Established Name:	Albuterol Sulfate Sterile Solution for Inhalation by Nebulizer, 0.5% (2.5 mg/0.5 mL)

Labeling Deficiencies:

1. CONTAINER – Unit-of-Use Plastic Vial (0.5 mL)
   Satisfactory in **draft** as of the February 16, 2000 submission

2. CARTON – Box of 30 Unit-of Use Vials
   Satisfactory in **draft** as of the March 29, 2001 submission

3. FOIL POUCH
   Satisfactory in **final print** as of the April 30, 2001 submission

4. INSERT:
   Satisfactory in **final print** as of the April 30, 2001 submission

Please prepare and submit **12 copies of final print** for your CONTAINER and CARTON labels.

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.htm

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

RECORD OF TELEPHONE CONVERSATION

Contacted Mr. Simmons and told him he needed to submit 12 copies of FPL for the carton and container. He told me he would FedEx them overnight.

V:\FIRMSNZ\NEPHRON\TELECONS\75-664telecon.doc

APPEARS THIS WAY
ON ORIGINAL

DATE
5/31/01

APPLICATION NUMBERS
75-664

IND NUMBER

TELECON

INITIATED BY
__APPLICANT / SPONSOR

X FDA

PRODUCT NAME
Albuterol Sulfate Sterile Soln.

FIRM NAME
Nephron Pharmaceuticals, Inc.

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Mr. Simmons

TELEPHONE NUMBER
407-246-1389

SIGNATURE

James T. Barlow

cc:

ANDA: 75-664
DUP/DIVISION FILE

Dillahunt, Michelle

From: Dillahunt, Michelle
Sent: Monday, June 04, 2001 4:01 PM
To: Wiseman, Rosemarie*; Green, Wayne*
Subject: ANDA 75-664 Albuterol-Nephron

Please change the micro amendment dated 5/15/01 to minor amendment assigned to chemistry and microbiology.

Thanks,
Michelle

ANDA NUMBER 75-664

FIRM: Nephron Pharmaceuticals Corp.

DOSAGE FORM: Solution

STRENGTH: 0.5% (2.5 mg/0.5 ml)

DRUG: Albuterol Sulfate

CGMP STATEMENT/EIR UPDATE STATUS: Acceptable 11/6/00.

BIO STUDY: The waiver of an *in vivo* bioequivalence study for the drug product was granted per the Division of Bioequivalence on 4/3/00.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

MVP for the applicant's drug product at a concentration of 0.083% (74-880) was satisfactory. The analytical methods for this drug product are the same as those for the applicant's approved product (Albuterol Sulfate Inhalation Solution, 0.083%). It was determined that the 0.5% solution is comparable to the 0.083% product when diluted properly. MV for this product is not necessary and is waived.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION? Yes

The [redacted] container/closure system is a one-piece construction. The container size is 0.8 ml. Each [redacted] ampule is individually protected from [redacted], manufactured by [redacted].

The dimensions of the individual foil pouch are:

	OUTSIDE (mm)	[redacted]
Length	150	
Width	57	

Data are provided for exhibit lot Z8088E (Original lot, [redacted].

3-Month data for samples stored at 40°C/75%RH and tested at 0, 1, 2 and 3-months.

24-Month data for samples stored at 25°C/60%RH.
24-Month data for samples stored at 2°C to 8°C.

Data are provided for exhibit lot Z0018E. Individual vials are packaged in [redacted]. This foil is approved for use with Albuterol Sulfate Inhalation Solution, 0.083% for ANDA
74-880.

3-Month data for samples stored at 40°C/75%RH and tested at 0, 1, 2 and 3-months.

9-Month data for samples stored at 25°C/60%RH.

9-Month data for samples stored at 2°C to 8°C.

A 3rd exhibit batch (Z0138) was packaged in the [redacted] and satisfactory 3 months accelerated data provided. [redacted] will be used for commercial product.

LABELING: Satisfactory per the June 11, 2001 review.

STERILIZATION VALIDATION (IF APPLICABLE):

The microbiologist's review #3 (May 29, 2001) recommended the submission for approval on the basis of sterility assurance.

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?): (Yes. DMF [redacted]

[redacted]

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

[redacted]s for lots Z8088 and Z0018. [redacted] for lot Z0138.

Same Process as Bio batch.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?

Same Process.

/S/ 6/25/01

Review Chemist:	Shirley S. Brown	6/18/01
Team Leader:	Michael Smela	6/18/01
Date:	June 18, 2001	

/S/ 6/25/01

V:\FIRMSNZ\NEPHRON\LTRS&REV\check75.664.doc
F/T by: DJ 6/19/01

APPEARS THIS WAY
ON ORIGINAL

APPROVAL SUMMARY

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

ANDA Number: 75-664
Date of Submission: ~~April 30, 2001~~ May 31, 2001
Applicant's Name: Nephron Pharmaceuticals Corporation
Established Name: Albuterol Sulfate Sterile Solution for Inhalation by Nebulizer, 0.5% (2.5 mg/0.5 mL)

APPROVAL SUMMARY

1. **Do you have 12 Final Printed Labels and Labeling?** Yes

2. **CONTAINER** – Unit-of-Use Plastic Vial (0.5 mL)
   Satisfactory in **final print** as of the February 16, 2000 submission
   (See blue volume 1.1; attachment 5-4 page 000064)

3. **CARTON** – Box of 30 Unit-of Use Vials
   Satisfactory in **final print** as of the May 31, 2001 submission
   (See blue volume 6.1)

4. **FOIL POUCH**
   Satisfactory in **final print** as of the April 30, 2001 submission
   (See blue volume 5.1, pages 12, 13 and 14)

5. **INSERT:**
   Satisfactory in **final print** as of the April 30, 2001 submission
   (See blue volume 5.1, pages 12, 13 and 14)

6. **Revisions needed post-approval**: None

7. **Patent Issues:** No patent issues exist at this time

BASIS OF APPROVAL:

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Proventil Solution for Inhalation 0.5%.
NDA Number: N 19-243
NDA Drug Name: Proventil Solution for Inhalation 0.5%.
NDA Firm: Schering Corporation; N 19-243/S-014; Approved March 13, 2000.
Date of Approval of NDA Insert and supplement : N 19-243/S-014; Approved March 13, 2000.
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: Most recently approved labeling of the reference listed drug.
Basis of Approval for the Carton Labeling: Most recently approved labeling of the reference listed drug.

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's 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 24**		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			
PROPRIETARY NAME			
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 -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR. **(Individual 2.5 mg/0.5mL unit-of-use containers packaged in cartons of 30 for concentrated albuterol 0.5%)**	x		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. [see FTR]		X	
Does the package proposed have any safety and/or regulatory concerns? **There were some concerns however, after meetings between Nephron Pharmaceutical and OGD they have** been resolved.		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	
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 (p. #) 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 p. # 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 bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD:

1. **Review was based on the labeling of the most recently approved labeling for the reference listed drug ;Proventil Solution for Inhalation 0.5%; approved March 13, 2000; 19-243/S-014.**
2. Patent/ Exclusivities:
   The patent that exist for this drug product has expired. The firm is filing paragraph II (see section 3.1 in volume A.2.1.)
3. Storage/Dispensing Conditions:
   NDA: Store between 2° - 25°C(36° - 77°F).
   ANDA: Same as RLD
4. Product Line:
   The innovator markets their 0.5% strength Albuterol Solution for Inhalation product in 20 mL glass amber bottles containing a calibrated dropper.

   The applicant proposes to market their product in plastic, sterile unit-of-use vials of 0.5 mL (2.5 mg/0.5mL) individually packed in a foil package available in cartons of 30 units.
5. Inactive Ingredients:
   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 148 Vol. 1.1.

6. **Note that the firm relocated the statements "DILUTE BEFORE USE" and " FOR ORAL INHALATION ONLY" to the front panel of the CARTON and is on the front panel of the POUCH. I feel that this was a good idea to alleviate some safety concerns. Also Note that the firm did NOT include the paragraph "** [redacted]

Date of Review: 6/11/01 Date of Submission: 5/31/01

Primary Reviewer: Jim Barlow Date: 6/12/01

Team Leader: John Grace Date: 6/14/2001

cc:

ANDA: 75-664
DUP/DIVISION FILE
HFD-613/JBarlow/JGrace (no cc)
V:\FIRMSNZ\NEPHRON\LTRS&REV\75664ap.s
Review

APPEARS THIS WAY
ON ORIGINAL

Search results from the "Rx" table for query on "019243."

Active Ingredient:	ALBUTEROL SULFATE
Dosage Form;Route:	Solution; Inhalation
Proprietary Name:	PROVENTIL
Applicant:	SCHERING
Strength:	EQ 0.5% BASE
Application Number:	019243
Product Number:	001
Approval Date:	Jan 14, 1987
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	**AN**
Patent and Exclusivity Info for this product:	Click Here

Active Ingredient:	ALBUTEROL SULFATE
Dosage Form;Route:	Solution; Inhalation
Proprietary Name:	PROVENTIL
Applicant:	SCHERING
Strength:	EQ 0.083% BASE
Application Number:	019243
Product Number:	002
Approval Date:	Jan 14, 1987
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	**AN**
Patent and Exclusivity Info for this product:	Click Here

Thank you for searching the **Electronic Orange Book**!

Return to Electronic Orange Book Home Page

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

Exclusivity Data

There is no unexpired exclusivity for this product.

Thank you for searching the Electronic Orange Book

Patent and Exclusivity Terms

Return to Electronic Orange Book Home Page

ANDA 75-664

OFFICE OF GENERIC DRUGS

Food and Drug Administration
HFD-600, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Fax: 301-594-0180

FAX TRANSMISSION COVER SHEET

TO: APPLICANT: Nephron Pharmaceuticals Corporation

ATTN: Steve Simmons

TEL: 407-246-1389

FAX: 407 872-0001

PROJECT MANAGER: 301-827-5848

FROM: Michelle Dillahunt

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated July 2, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Albuterol Sulfate Inhalation Solution, 0.5% (base), packaged in 2.5 mg/0.5 mL Unit of-Use Vials.

We are pleased to inform you that this application is APPROVED!

Verified 12/26/2001 Rw Scott

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **ANDA 75664/000**
Stamp: **06-JUL-1999** Regulatory Due:
Applicant: **NEPHRON**
4121 SOUTHWEST 34TH ST
ORLANDO, FL 328116458

Priority:
Action Goal:
Brand Name:
Established Name: **ALBUTEROL SULFATE**
Generic Name:
Dosage Form: **SOL (SOLUTION)**
Strength: **0.5%**

Org Code: **600**
District Goal: **06-JUN-2000**

FDA Contacts: **M. DILLAHUNT (HFD-613) 301-827-5848 , Project Manager**
M. SMELA JR (HFD-625) 301-827-5848 , Team Leader

Overall Recommendation:

ACCEPTABLE on 06-NOV-2000 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: [redacted]
DMF No: [redacted]
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **02-MAR-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: [redacted]

Establishment: [redacted]
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **02-MAR-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: [redacted]

Establishment: **1054871**
NEPHRON PHARMACEUTICALS COI
4121 SOUTHWEST 34TH ST
ORLANDO, FL 328116458
DMF No:
AADA No:

Profile: **LIQ** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **06-NOV-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Establishment: [redacted]

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **02-MAR-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: [redacted]

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-664

CORRESPONDENCE

nephron
pharmaceuticals
corporation
SINCE 1937

Office of Generic Drugs (HFD-600)
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT
N/AF FPL

MAY 3 1 2001

REFERENCE: Additonal Labeling Requested for ANDA 75-664

Gentlemen:

Attached, please find additional labeling as requested by the Labeling Review Branch. We are forwarding 11 copies of the carton artwork which were supplied to the carton manufacturer, and 1 printer's proof of the cartons being produced. This information is provide to support our Abbreviated New Drug Application 75-664 for the production of Albuterol Sulfate Inhalation Solution, 0.5%, as outlined below.

1. PURPOSE OF THE SUBMISSION:

   To provide the labeling reviewer with additional materials, as requested. Nephron's proposed drug product is Albuterol Sulfate Inhalation Solution, 0.5%. Nephron's goal is to gain approval from the Food and Drug Administration for the production of the proposed drug product at Nephron's manufacturing facility in Orlando, Florida. The proposed drug product is an orally administered bronchodilator, in sterile form, in a single, unit-of-use 0.5 mL container, packaged individually in a foil pouch overwrap. Thirty of these individually wrapped units is provided per carton.

2. TYPE OF SUBMISSION: This submission is additional information, as requested to support an Abbreviated New Drug Application.

3. PROPRIETARY NAME: None. The generic drug name will be used.

4. NUMBER OF VOLUMES SUBMITTED: 1 Archive Copy, containing 1 volumes
   1 Review Copy, containing 1 volumes
   1 Field Submission Copy, containing 1 volumes, (submitted to the Orlando District)

5. THIRD COPY CERTIFICATION STATEMENT: We certify that the third (field) copy of this Abbreviated New Drug Application contains a true copy of all sections, both administrative and technical and has been sent directly to the Orlando District Office.

6. Rx / OTC DRUG STATEMENT: This application is for the production of a prescription drug product (Rx).

4121 34th Street Orlando, FL 32811 (407) 246-1389

7. FACILITY PERSONNEL: The following Nephron Pharmaceuticals Corporation personnel are available to answer questions concerning this submission:

Administration:	Steven F. Simmons, President
Quality Assurance:	J. Brian Lundberg, Director of Quality Assurance
Quality Control:	Angel Pérez, Manager - Quality Control, Chemistry
	Karen Pendleton, Manager - Quality Control, Microbiology
Production:	Raúl Lugo, Manager - Production

8. CONSULTANTS: The following consultants are authorized to act on behalf of Nephron Pharmaceuticals Corporation concerning this ANDA, in the following capacities:

Outside Counsel:

David L. Rosen, R.Ph., J.D.
Attorney at Law
McDermott, Will & Emery
600 13th St, N.W.
Washington, DC 20005-3096
(202) 756-8075

[redacted]

[redacted]

We appreciate the agency's expedient review of our application, and look forward to an early reply.

Sincerely,

NEPHRON PHARMACEUTICALS CORP.

Steven F. Simmons
President

nephron
pharmaceuticals
corporation
SINCE 1937

Office of Generic Drugs (HFD-600)
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

MAY 15 2001

ORIG AMENDMENT
N/AM

REFERENCE: MINOR AMENDMENT to ANDA 75-664

Gentlemen:

Attached, please find our response to the Microbiology deficiencies found during review of our Abbreviated New Drug Application 75-664 for the production of Albuterol Sulfate Inhalation Solution, 0.5%, as outlined below.

1. PURPOSE OF THE SUBMISSION:

   To address the minor deficiencies found in the microbiology review for the proposed drug product, Albuterol Sulfate Inhalation Solution, 0.5%. Nephron's goal is to gain approval from the Food and Drug Administration for the production of the proposed drug product at Nephron's manufacturing facility in Orlando, Florida. The proposed drug product is an orally administered bronchodilator, in sterile form, in a single-use 0.5 mL [redacted] container, packaged individually in a foil pouch overwrap.

2. TYPE OF SUBMISSION: This submission is a Minor Amendment to an Abbreviated New Drug Application.

3. PROPRIETARY NAME: None. The generic drug name will be used.

4. NUMBER OF VOLUMES SUBMITTED: 1 Archive Copy, containing 2 volumes
   1 Review Copy, containing 2 volumes
   1 Field Submission Copy, containing 2 volumes, (submitted to the Orlando District)

5. THIRD COPY CERTIFICATION STATEMENT: We certify that the third (field) copy of this Abbreviated New Drug Application contains a true copy of all sections, both administrative and technical and has been sent directly to the Orlando District Office.

6. Rx / OTC DRUG STATEMENT: This application is for the production of a prescription drug product (Rx).

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
MAY 16 2001
OGD

4121 34th Street Orlando, FL 32811 (407) 246-1389

7. FACILITY PERSONNEL: The following Nephron Pharmaceuticals Corporation personnel are available to answer questions concerning this submission:

Administration:	Steven F. Simmons, President
Quality Assurance:	J. Brian Lundberg, Director of Quality Assurance
Quality Control:	Angel Pérez, Manager - Quality Control, Chemistry
	Karen Pendleton, Manager - Quality Control, Microbiology
Production:	Raúl Lugo, Manager - Production

8. CONSULTANTS: The following consultants are authorized to act on behalf of Nephron Pharmaceuticals Corporation concerning this ANDA, in the following capacities:

Outside Counsel: David L. Rosen, R.Ph., J.D.
Attorney at Law
McDermott, Will & Emery
600 13th St, N.W.
Washington, DC 20005-3096
(202) 756-8075

[redacted]

[redacted]

We appreciate the agency's expedient review of our application, and look forward to an early reply.

Sincerely,

NEPHRON PHARMACEUTICALS CORP.

Steven F. Simmons
President

nephron
pharmaceuticals
corporation
SINCE 1937

Office of Generic Drugs (HFD-600)
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

APR 3 0 2001

ORIG AMENDMENT

N/AF

REFERENCE: Minor Amendment – Labeling for ANDA 75-664

Gentlemen:

Attached, please find our Minor Amendment addressing Labeling deficiencies during review of our Abbreviated New Drug Application 75-664 for the production of Albuterol Sulfate Inhalation Solution, 0.5%, as outlined below.

1. PURPOSE OF THE SUBMISSION:

   To address labeling deficiencies found during review for the proposed drug product, Albuterol Sulfate Inhalation Solution, 0.5%. Nephron's goal is to gain approval from the Food and Drug Administration for the production of the proposed drug product at Nephron's manufacturing facility in Orlando, Florida. The proposed drug product is an orally administered bronchodilator, in sterile form, in a single-use 0.5 mL [redacted] container, packaged individually in a foil pouch overwrap.

2. TYPE OF SUBMISSION: This submission is a Minor Amendment to an Abbreviated New Drug Application.

3. PROPRIETARY NAME: None. The generic drug name will be used.

4. NUMBER OF VOLUMES SUBMITTED: 1 Archive Copy, containing 1 volumes
   1 Review Copy, containing 1 volumes
   1 Field Submission Copy, containing 1 volumes, (submitted to the Orlando District)

5. THIRD COPY CERTIFICATION STATEMENT: We certify that the third (field) copy of this Abbreviated New Drug Application contains a true copy of all sections, both administrative and technical and has been sent directly to the Orlando District Office.

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RECD
MAY 0 1 2001
OGD

6. Rx / OTC DRUG STATEMENT: This application is for the production of a prescription drug product (Rx).

4121 34th Street Orlando, FL 32811 (407) 246-1389

7. FACILITY PERSONNEL: The following Nephron Pharmaceuticals Corporation personnel are available to answer questions concerning this submission:

Administration:	Steven F. Simmons, President
Quality Assurance:	J. Brian Lundberg, Director of Quality Assurance
Quality Control:	Angel Pérez, Manager - Quality Control, Chemistry
	Karen Pendleton, Manager - Quality Control, Microbiology
Production:	Raúl Lugo, Manager - Production

8. CONSULTANTS: The following consultants are authorized to act on behalf of Nephron Pharmaceuticals Corporation concerning this ANDA, in the following capacities:

Outside Counsel:

David L. Rosen, R.Ph., J.D.
Attorney at Law
McDermott, Will & Emery
600 13th St, N.W.
Washington, DC 20005-3096
(202) 756-8075

[redacted]

We appreciate the agency's expedient review of our application, and look forward to an early reply.

Sincerely,

NEPHRON PHARMACEUTICALS CORP.

Steven F. Simmons
President

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
MAY 01 2001
OGD

nephron
pharmaceuticals
corporation
SINCE 1937

Office of Generic Drugs (HFD-600)
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT
APR 17 2001

REFERENCE: Telephonic Amendment to ANDA 75-664

Gentlemen:

Attached, please find our Telephonic Amendment addressing Chemistry deficiencies acknowledged by Mr. Mike Smela and Ms. Shirley Brown, during review of our Abbreviated New Drug Application 75-664 for the production of Albuterol Sulfate Inhalation Solution, 0.5%, as outlined below.

1. PURPOSE OF THE SUBMISSION:

   To address minor deficiencies found in the chemistry review for the proposed drug product, Albuterol Sulfate Inhalation Solution, 0.5%. Nephron's goal is to gain approval from the Food and Drug Administration for the production of the proposed drug product at Nephron's manufacturing facility in Orlando, Florida. The proposed drug product is an orally administered bronchodilator, in sterile form, in a single-use 0.5 mL [redacted] container, packaged individually in a foil pouch overwrap.

2. TYPE OF SUBMISSION: This submission is a Telephonic Amendment to an Abbreviated New Drug Application.

3. PROPRIETARY NAME: None. The generic drug name will be used.

4. NUMBER OF VOLUMES SUBMITTED: 1 Archive Copy, containing 1 volumes
   1 Review Copy, containing 1 volumes
   1 Field Submission Copy, containing 1 volumes,
   (submitted to the Orlando District)

5. THIRD COPY CERTIFICATION STATEMENT: We certify that the third (field) copy of this Abbreviated New Drug Application contains a true copy of all sections, both administrative and technical and has been sent directly to the Orlando District Office.

6. Rx / OTC DRUG STATEMENT: This application is for the production of a prescription drug product (Rx).

CENTER FOR DRUG
RECD
APR 18 2001
OGD
EVALUATION AND RESEARCH

75-664

4121 34th Street Orlando, FL 32811 (407) 246-1389

7. FACILITY PERSONNEL: The following Nephron Pharmaceuticals Corporation personnel are available to answer questions concerning this submission:

Administration:	Steven F. Simmons, President
Quality Assurance:	J. Brian Lundberg, Director of Quality Assurance
Quality Control:	Angel Pérez, Manager - Quality Control, Chemistry
	Karen Pendleton, Manager - Quality Control, Microbiology
Production:	Raúl Lugo, Manager - Production

8. CONSULTANTS: The following consultants are authorized to act on behalf of Nephron Pharmaceuticals Corporation concerning this ANDA, in the following capacities:

Outside Counsel:

David L. Rosen, R.Ph., J.D.
Attorney at Law
McDermott, Will & Emery
600 13th St, N.W.
Washington, DC 20005-3096
(202) 756-8075

[redacted]

[redacted]

We appreciate the agency's expedient review of our application, and look forward to an early reply.

Sincerely,

NEPHRON PHARMACEUTICALS CORP.

Steven F. Simmons
President

CENTER FOR DRUG
RECD
APR 18 2001
OGD
EVALUATION AND RESEARCH

nephron
pharmaceuticals
corporation
SINCE 1937

Office of Generic Drugs (HFD-600)
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

MAR 2 9 2001

REFERENCE: Minor Amendment to ANDA 75-664

Gentlemen:

Attached, please find our response to the Microbiology and Chemistry deficiencies found during review of our Abbreviated New Drug Application 75-664 for the production of Albuterol Sulfate Inhalation Solution, 0.5%, as outlined below.

1. PURPOSE OF THE SUBMISSION:

   To address the minor deficiencies found in the microbiology and chemistry review for the proposed drug product, Albuterol Sulfate Inhalation Solution, 0.5%. Nephron's goal is to gain approval from the Food and Drug Administration for the production of the proposed drug product at Nephron's manufacturing facility in Orlando, Florida. The proposed drug product is an orally administered bronchodilator, in sterile form, in a single-use 0.5 mL container, packaged individually in a foil pouch overwrap.

2. TYPE OF SUBMISSION: This submission is a Minor Amendment to an Abbreviated New Drug Application.

3. PROPRIETARY NAME: None. The generic drug name will be used.

4. NUMBER OF VOLUMES SUBMITTED: 1 Archive Copy, containing 2 volumes
   1 Review Copy, containing 2 volumes
   1 Field Submission Copy, containing 2 volumes, (submitted to the Orlando District)

5. THIRD COPY CERTIFICATION STATEMENT: We certify that the third (field) copy of this Abbreviated New Drug Application contains a true copy of all sections, both administrative and technical and has been sent directly to the Orlando District Office.

6. Rx / OTC DRUG STATEMENT: This application is for the production of a prescription drug product (Rx).

CENTER FOR DRUG EVALUATION AND RESEARCH
MAR 30 2001
OGD

4121 34th Street Orlando, FL 32811 (407) 246-1389

7. FACILITY PERSONNEL: The following Nephron Pharmaceuticals Corporation personnel are available to answer questions concerning this submission:

Administration:	Steven F. Simmons, President
Quality Assurance:	J. Brian Lundberg, Director of Quality Assurance
Quality Control:	Angel Pérez, Manager - Quality Control, Chemistry
	Karen Pendleton, Manager - Quality Control, Microbiology
Production:	Raúl Lugo, Manager - Production

8. CONSULTANTS: The following consultants are authorized to act on behalf of Nephron Pharmaceuticals Corporation concerning this ANDA, in the following capacities:

Outside Counsel:

David L. Rosen, R.Ph., J.D.
Attorney at Law
McDermott, Will & Emery
600 13th St, N.W.
Washington, DC 20005-3096
(202) 756-8075

[redacted]

We appreciate the agency's expedient review of our application, and look forward to an early reply.

Sincerely,

NEPHRON PHARMACEUTICALS CORP.

Steven F. Simmons
President

Received
FDA Stmt 2/12/01

nephron pharmaceuticals corporation
SINCE 1937

February 12, 2001

Subject to Review 3/29/01
Addt 5/10/01

ANDA 75-664

NEW CORRESP

VIA HAND DELIVERY

Mr. Gary Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
United States Food and Drug Administration
Metro Park North 2
7500 Standish Place
Rockville, MD 20855-2773

Re: Validation Reports and Related Background Information Regarding Microbiology Deficiency on ANDA 75-664, Albuterol Sulfate Inhalation Solution, 0.5%

For Telephone Conference February 14, 2001 at 10:00 am.

Dear Mr. Buehler,

Enclosed please find validation data and background information to respond to the microbiology deficiency identified during the review of our ANDA 75-664, Albuterol Sulfate Inhalation Solution, 0.5%. We firmly believe that the enclosed data supports our position that the 'holding period' of 6 days is fully validated and appropriate.

We look forward to the telephone conference on Wednesday, February 14, 2001 at 10:00am to discuss and expeditiously resolve this matter so that our application can be approved.

The call in number for the conference call is 1-800-811-2539.
The participant code is 743450.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
FEB 12 2001
OGD

4121 34th Street Orlando, FL 32811 (407) 246-1389

I appreciate your review of the enclosed material and to our discussion on Wednesday.

Sincerely,

Steven F. Simmons

Steven F. Simmons

nephron
pharmaceuticals
corporation
SINCE 1937

January 12, 2001

NEW CORRESP

ANDA 75-664

VIA FACSIMILE AND EXPRESS MAIL

Mr. Gary Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
United States Food and Drug Administration
Metro Park North 2
7500 Standish Place
Rockville, MD 20855-2773

Re: Request for Meeting Concerning Microbiology Deficiency on ANDA 75-664, Albuterol Sulfate Inhalation Solution, 0.5%

Dear Mr. Buehler,

I am writing you to request that a meeting be scheduled as soon as possible to discuss an important matter that has arisen during the review of our ANDA 75-664, Albuterol Sulfate Inhalation Solution, 0.5%. During the microbiology review of the above ANDA (see copy attached), the reviewer states the following as a deficiency:

[ ]

that follow:

[ ]

4121 34th Street Orlando, FL 32811 (407) 246-1389

[redacted]

Finally, the product [redacted] process has been previously approved by FDA in ANDA 74-880 on September 17, 1997. The process has also been reviewed by investigators of the Orlando District Office during preapproval inspections for Albuterol Sulfate Inhalation Solution 0.083% and 0.5%, as well as Ipratropium Bromide Inhalation Solution, 0.02%, and no comments or observations were noted.

As you likely understand, we were quite surprised that OGD has raised an issue concerning our fully validated process. Due to the potential impact of this deficiency identified by the OGD reviewing Microbiologist, Nephron requests that the meeting be held as soon as possible, within the next 30 days so that review of the pending ANDA is not substantially delayed. Either Mr. Rosen or I will contact your office early next week to schedule such a meeting.

Further, Nephron requests that the microbiology reviewer provide scientific evidence supporting the request for a maximum process time of 48 hours. In addition, Nephron requests clarification for being instructed to ignore their previous validation, which was conducted in compliance with FDA's published guidelines on process validation.

Personnel attending from Nephron Pharmaceuticals Corporation will be:

Steven F. Simmons
President

J. Brian Lundberg
Director – Quality Assurance

Karen Pendleton
Manager, Q.C. Microbiology

Outside Consultants

[redacted]

David Rosen, R.Ph., J.D.
McDermott, Will & Emery

* * * * * * * * *

I appreciate your prompt review of this matter and look forward to your assistance in scheduling a meeting as soon as possible so that the issue can be resolved and the application can be approved expeditiously.

Sincerely,

Steven F. Simmons

nephron
pharmaceuticals
corporation
SINCE 1937

Office of Generic Drugs (HFD-600)
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

JUL 2 0 2000

NDA ORIG AMENDMENT
AA

REFERENCE: Amendment to ANDA 75-664
for Albuterol Sulfate Inhalation Solution, 0.5%

Gentlemen:

Attached, please find our Amendment to Abbreviated New Drug Application 75-664 for the production of Albuterol Sulfate Inhalation Solution, 0.5%, as outlined below.

1. PURPOSE OF THE SUBMISSION:

   Nephron's goal is to gain approval from the Food and Drug Administration for the production of Albuterol Sulfate Inhalation Solution, 0.5% at Nephron's current facility in Orlando, Florida. The proposed drug product is an orally administered bronchodilator, in sterile form, in a single-use 0.5 mL container, packaged individually in a foil pouch overwrap.

   Nephron presently has an application for Ipratropium Bromide Inhalation Solution 0.02% (ANDA 75-562), being reviewed by the FDA. On June 12, 2000, a deficiency letter for microbiology issues related to the application was faxed to Nephron. Nephron's response to the issues was submitted to FDA on July 6, 2000.

   Since many of the issues addressed are of a general nature and relate to the production of oral inhalation solution products, Nephron is being proactive and answering the deficiencies as they may pertain to ANDA 75-664. In so doing, Nephron hopes to provide the microbiology reviewer with necessary information and reduce the required review time.

   In addition to the microbiology issues, Nephron is also submitting additional room temperature test data for the exhibit batch up through the 18 month test interval.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUL 2 1 2000
OGD

2. TYPE OF SUBMISSION: This submission is an Abbreviated New Drug Application.

3. PROPRIETARY NAME: None. The generic drug name will be used.

4. NUMBER OF VOLUMES SUBMITTED: 1 Archive Copy, containing 1 volume
   1 Review Copy, containing 1 volume
   1 Field Submission Copy, containing 1 volume,
   (submitted to the Orlando District)

5. THIRD COPY CERTIFICATION STATEMENT: We certify that the third (field) copy of this Abbreviated New Drug Application contains a true copy of all sections, both administrative and technical and has been sent directly to the Orlando District Office.

4121 34th Street Orlando, FL 32811 (407) 246-1389

6. Rx / OTC DRUG STATEMENT: This application is for the production of a prescription drug product (Rx).

7. FACILITY PERSONNEL: The following Nephron Pharmaceuticals Corporation personnel are available to answer questions concerning this submission:

Administration:	Steven F. Simmons, President
Quality Assurance:	J. Brian Lundberg, Director of Quality Assurance
Quality Control:	Angel Pérez, Manager - Quality Control, Chemistry
	Karen Pendleton, Manager - Quality Control, Microbiology
Production:	Raúl Lugo, Manager - Production

8. CONSULTANTS: The following consultants are authorized to act on behalf of Nephron Pharmaceuticals Corporation concerning this ANDA, in the following capacities:

Outside Counsel:
David L. Rosen, R.Ph., J.D.
Attorney at Law
McDermott, Will & Emery
600 13th St, N.W.
Washington, DC 20005-3096
(202) 756-8075

[redacted]

We appreciate the agency's expedient review of our application, and look forward to an early reply.

Sincerely,

NEPHRON PHARMACEUTICALS CORP.

Steven F. Simmons
President

ANDA 75-664

Nephron Pharmaceuticals Corp.
Attention: Steven F. Simmons
4121 34th Street
Orlando, FL 32811-6458

MAR 2

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.

Reference is made to our "Refuse to File" letter dated August 13, 1999 and your amendment dated February 16, 2000.

NAME OF DRUG: Albuterol Sulfate Inhalation Solution, 0.5%

DATE OF APPLICATION: July 2, 1999

DATE (RECEIVED) ACCEPTABLE FOR FILING: February 17, 2000

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

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

Should you have questions concerning this application, contact:

Michelle Dillahunt
Project Manager
(301) 827-5848

Sincerely yours,

/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

nephron pharmaceuticals corporation
SINCE 1937

505(j)(2)(A) OK
/S/ 2/28/00
/S/

Office of Generic Drugs (HFD-600)
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

FEB 16 2000

ORIG AMENDMENT
N/A C

REFERENCE: Ammendment to ANDA 75-664
Albuterol Sulfate Inhalation Solution, 0.5%

Gentlemen:

Attached, please find our amendment to ANDA 75-664 for the production of Albuterol Sulfate Inhalation Solution, 0.5%, as outlined below.

1. PURPOSE OF THE SUBMISSION: To withdraw the previously submitted Reference Listed Drug (RLD), and submit a new RLD.

   Nephron's original submission of July 2, 1999 cited Glaxo's Ventolin® (albuterol sulfate) Inhalation Solution 0.5%, as the RLD. Following Nephron's meeting with CDER on November 3, 1999, and a CDER committee meeting on February 9, 2000, a recommendation was made by the committee that Nephron amend its application and resubmit Schering's Proventil (albuterol sulfate) inhalation solution, 0.5% as the new RLD. Since the formulations of the two products are identical, no significant change to the application is required with the exception of the change to those sections of the application referencing the RLD.

   The unit-of-use container nomenclature used in this application is supported by correspondence from OGD/CDER dated April 19, 1999. A copy of the correspondence from Mr. Douglas Sporn's office is attached.

   As previously submitted, Nephron's proposed drug product is an orally administered bronchodilator, in sterile form, whose primary packaging is in a unit-of-use 1 mL, (0.5mL fill) [redacted] container, and secondary packaging of [redacted] foil pouch.

   Although Nephron is currently producing additional exhibit batches which package one unit-of-use vial in an individual pouch, it is Nephron's understanding that the previously submitted stability data for the proposed drug product, packaged as 30 unit-of-use vials in a foil pouch, is adequate, and will be used to meet the stability requirements for this application.

   The facility, equipment, and processes used to manufacture this product are the same as those used to manufacture albuterol sulfate inhalation solution 0.083% previously approved under ANDA 74-880 on September 17, 1997. The facility received a satisfactory GMP inspection from the Orlando District Office in August 1997.

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RECD
FEB 17 2000
OGD

4121 34th Street Orlando, FL 32811 (407) 246-1389

The active ingredient (albuterol sulfate) and [redacted] is the same active ingredient and supplier previously approved under ANDA 74-880. The container component ([redacted]) and [redacted]) is the same component and supplier previously approved under ANDA 74-880. The analytical method of analysis is the same as that approved under ANDA 74-880 with the exception of the sample dilution since the analyte concentration is 0.5%.

2. TYPE OF SUBMISSION: This submission is an amendment to an Abbreviated New Drug Application.

3. PROPRIETARY NAME: None. The generic drug name will be used.

4. NUMBER OF VOLUMES SUBMITTED: 1 Archive Copy, containing 2 volumes
   1 Review Copy, containing 2 volumes
   1 Field Submission Copy, containing 2 volumes, (submitted to the Orlando District)

5. THIRD COPY CERTIFICATION STATEMENT: We certify that the third (field) copy of this Abbreviated New Drug Application contains a true copy of all sections, both administrative and technical and has been sent directly to the Orlando District Office.

6. Rx / OTC DRUG STATEMENT: This application is for the production of a prescription drug product (Rx).

7. FACILITY PERSONNEL: The following Nephron Pharmaceuticals Corporation personnel are available to answer questions concerning this submission:

Administration:	Steven F. Simmons, President
Quality Assurance:	J. Brian Lundberg, Director of Quality Assurance
Quality Control:	Angel Pérez, Manager - Quality Control, Chemistry
	Karen Pendleton, Manager - Quality Control, Microbiology
Production:	Raúl Lugo, Manager - Production

8. CONSULTANTS: The following consultants are authorized to act on behalf of Nephron Pharmaceuticals Corporation concerning this ANDA, in the following capacities:

Outside Counsel:
David L. Rosen, R.Ph., J.D.
Attorney at Law
McDermott, Will & Emery
600 13th St, N.W.
Washington, DC 20005-3096
(202) 756-8075

We appreciate the agency's expedient review of our application, and look forward to an early reply.

Sincerely,

NEPHRON PHARMACEUTICALS CORP.

Steven F. Simmons
President

APPEARS THIS WAY
ON ORIGINAL

nephron
pharmaceuticals
corporation
SINCE 1937

FEB 16 2000

Office of Generic Drugs (HFD-600)
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

REFERENCE: Field Copy Certification Statement

Gentlemen:

We certify that the field copy of this Ammendment to Abbreviated New Drug Application 75-664 contains a true copy of all sections, both administrative and technical and has been sent directly to the Orlando District Office.

Sincerely,

NEPHRON PHARMACEUTICALS CORP.

Steven F. Simmons
President

4121 34th Street Orlando, FL 32811 (407) 246-1389

nephron
pharmaceuticals
corporation
SINCE 1937

February 3, 2000

NEW CORRESP

Gregory Davis
Office of Generic Drugs (HFD-615)
CDER, FDA
7500 Standish Place
Metro Park North II
Rockville, MD 20855

REF: ANDA 75-664

Dear Mr. Davis,

In anticipation of your meeting this week, Nephron would like to have the following items discussed and commented upon by the committee concerning our application for Albuterol Sulfate Inhalation Solution, 0.5%, 0.5 mL and [redacted] Nephron would appreciate receiving timely comments and feedback resulting from the meeting.

1. We have expanded the proposed labeling to include both the 0.5 mL single unit-of-use package size for adult use, and the [redacted]. The proposed labeling is attached for comment.

2. Nephron's original application was filed on July 2, 1999. The manufacturing process of this product is the same as that of the Nephron's previously approved ANDA 74-880 which was cited in the application.. The changes being discussed do not significantly impact the application, since the application will be designated as an ANDA, as submitted by Nephron.

   The review of Nephron's application could have been undertaken with labeling review completed later, since no changes are to be made in the product formulation, components, or primary packaging [redacted] container). As a small business with few products, this delay significantly impacts Nephron business. Nephron requests that upon submission of its amendment, addressing labeling concerns, the review be undertaken and completed with all punctuality.

3. Should additional stability data for any modified packaging be required, Nephron will agree to prepare additional exhibit batches and place them into our accelerated and room temperature stability programs.

4121 34th Street Orlando, FL 32811 (407) 246-1389

Nephron will submit an amendment at the 90 day accelerated test station to provide this data to the reviewer, and thereby not delay review of the application. Nonetheless, we firmly believe that the stability data, (30 vials per foil pouch), included in the ANDA fully supports the stability of the product. Packaging a single unit-of-use vial in a foil pouch will not adversely impact the stability of the product.

I trust that the agency will proceed with the review and approval of our application in a most expedient manner. Thank you for your consideration.

Sincerely,

Steven F. Simmons
President

Enclosures (10)

nephron pharmaceuticals corporation
SINCE 1937

Meeting request converted to control document.
Given to R. Hassall 9/10/99

SEP 0 3 1999

NEW CORRESPONDENCE

Office of Generic Drugs (HFD-600)
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

REFERENCE: Major Amendment to ANDA 75-664
Albuterol Sulfate Inhalation Solution, 0.5%

Gentlemen:

Attached, please find our amendment to Abbreviated New Drug Application 75-664 for the production of Albuterol Sulfate Inhalation Solution, 0.5%, as outlined below.

1. PURPOSE OF THE SUBMISSION: To gain approval from the Food and Drug Administration for the production of albuterol sulfate inhalation solution, 0.5% at Nephron's current facility in Orlando, Florida. The proposed drug product is an orally administered bronchodilator, in sterile form, in a unit-of-use 1 mL, (0.5mL fill) [redacted] container, packaged 30 vials to a foil pouch.

   The unit-of-use container nomenclature used in this application is supported by correspondence from OGD/CDER dated April 19, 1999. A copy of the correspondence from Mr. Sporn's Office was previously submitted with the original application..

   The facility, equipment, and processes used to manufacture this product are the same as those used to manufacture albuterol sulfate inhalation solution 0.083% previously approved under ANDA 74-880 on September 17, 1997. The facility received a satisfactory GMP inspection from the Orlando District Office in July, 1999.

   The active ingredient (albuterol sulfate) and [redacted] is the same active ingredient and supplier previously approved under ANDA 74-880. The container component [redacted] e) and [redacted] is the same component and supplier previously approved under ANDA 74-880. The analytical method of analysis is the same as that approved under ANDA 74-880 with the exception of the analyte concentration which is 0.5%.

CENTER FOR DRUG
REC'D
SEP 0 8 1999
OGD
EVALUATION AND RESEARCH

4121 34th Street Orlando, FL 32811 (407) 246-1389

2. TYPE OF SUBMISSION: This submission is an Amendment to an Abbreviated New Drug Application.

3. PROPRIETARY NAME: None. The generic drug name will be used.

4. NUMBER OF VOLUMES SUBMITTED: 1 Archive Copy, containing 1 volume
   1 Review Copy, containing 1 volume
   1 Field Submission Copy, containing 1 volume,
   (submitted to the Orlando District)

5. THIRD COPY CERTIFICATION STATEMENT: We certify that the third (field) copy of this Abbreviated New Drug Application contains a true copy of all sections, both administrative and technical and has been sent directly to the Orlando District Office.

6. Rx / OTC DRUG STATEMENT: This application is for the production of a prescription drug product (Rx).

7. FACILITY PERSONNEL: The following Nephron Pharmaceuticals Corporation personnel are available to answer questions concerning this submission:

Administration:	Steven F. Simmons, President
Quality Assurance:	J. Brian Lundberg, Director of Quality Assurance
Quality Control:	Angel Pérez, Manager - Quality Control, Chemistry
	Karen Pendleton, Manager - Quality Control, Microbiology
Production:	Raúl Lugo, Manager - Production

8. CONSULTANTS: The following consultants are authorized to act on behalf of Nephron Pharmaceuticals Corporation concerning this ANDA, in the following capacities:

Outside Counsel:

David L. Rosen, R.Ph., J.D.
Attorney at Law
McDermott, Will & Emery
600 13th St, N.W.
Washington, DC 20005-3096
(202) 756-8075

We appreciate the agency's expedient review of our application, and look forward to an early reply.

Sincerely,

NEPHRON PHARMACEUTICALS CORP.

Steven F. Simmons
President

- request for meeting

Deficiency #1

The Office of Generic Drugs (OGD) consulted with the Division of Pulmonary Drug Products (DPDP), in the Office of Review Management. OGD, in agreement with DPDP, does not recommend the acceptance of your drug product as a generic for the following reasons:

> *OGD has safety concerns regarding a product that is packaged for single use but requires further dilution.*
>
> *DPDP representatives stated that the most acceptable configuration for such a "unit of use" product would be that each single unit of albuterol inhalation solution, 0.5% would be packaged with a unit of saline of a volume required for dilution."*

Response

Nephron disagrees with the conclusions of OGD and DPDP. This product, for all practical purposes, is no different from the product which is used by patients which is packaged in multiple dose containers. Patients must be trained by physicians, pharmacists, technicians, etc. to use the product, and similarly, our product would be adequately labeled with instructions for appropriate use.

A request for an informal meeting under 21 CFR §314.101 has been submitted. A copy of the request is attached.

nephron
pharmaceuticals
corporation
SINCE 1937

NC
NEW CORRESP

SEP 0 3 1999

Douglas Sporn, Director
Office of Generic Drugs (HFD-600)
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

REFERENCE: ANDA 75-664

Request for Informal Meeting

Dear Mr. Sporn:

In accordance with 21 CFR § 314.101(a)(3), Nephron Pharmaceuticals Corporation hereby requests an informal meeting be held to discuss the Agency's refusal to accept to file ANDA 75-664 for albuterol sulfate inhalation solution, 0.5% packaged in unit-of-use vials.

Specifically, Nephron desires to discuss the Office of Generic Drugs and Division of Pulmonary Drug Products decision that Albuterol Sulfate Inhalation Solution 0.5%, packaged in 0.5 mL unit-of-use containers is a danger to public safety. It is Nephron's firm belief that production of this product in the proposed container provides benefits to the public and does not raise safety concerns. The benefits are as follows:

1. The proposed drug product is a sterile drug product as opposed to the non-sterile multi-dose containers currently on the market.
2. The proposed drug product is free of preservatives [redacted], known to cause potential allergic reactions which may pose a danger to patients with pulmonary disorders.
3. The proposed drug product unit-of-use dispensing provides additional assurance against microbial contamination as opposed to the non-sterile drug products, which have increased bioburden with each successive entry of the bottle by the dropper.

It is our firm belief that the public will use the medication as labeled. In our view, the Agency's concern that the public will not dilute the medication prior to administration is unfounded. We strongly believe that the public will follow instructions to dilute the medication prior to use.

NW 9-9-99

4121 34th Street Orlando, FL 32811 (407) 246-1389

Nephron requests that the following personnel attend the meeting:

William P. Kennedy
Chief Executive Officer
Nephron Pharmaceuticals Corporation

Steven F. Simmons
President
Nephron Pharmaceuticals Corporation

J. Brian Lundberg
Director of Quality Assurance
Nephron Pharmaceuticals Corporation

David L. Rosen, R.Ph., J.D.
Regulatory Counsel
McDermott, Will & Emery

James C. Morrisson
Ombudsman
CDER, FDA

Office of Generic Drug Staff

Pulmonary Drug Staff

We appreciate the agency's expedient review of our request, and look forward to an early reply.

Sincerely,

NEPHRON PHARMACEUTICALS CORP.

Steven F. Simmons
President

Cc: David Rosen
Jim Morrison

ANDA 75-664

AUG 13 1999

Nephron Pharmaceuticals Corp.
Attention: Steven F. Simmons
4121 34th Street
Orlando, FL 32811-6458

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated July 2, 1999, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Albuterol Sulfate Inhalation Solution, 0.5%

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

The Office of Generic Drugs (OGD) consulted with the Division of Pulmonary Drug Products (DPDP), in the Office of Review Management. OGD, in agreement with DPDP, does not recommend the acceptance of your drug product as a generic for the following reasons:

OGD has safety concerns regarding a product that is packaged for single use but requires further dilution.

DPDP representatives stated that the most acceptable configuration for such a "unit of use" product would be that each single unit of albuterol inhalation solution, 0.5% would be packaged with a unit of saline of a volume required for dilution.

In addition, we are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

You have failed to provide a signed, dated letter of authorization from the drug master file (DMF) holder, [redacted] that allows [redacted] to act as agent in granting the Agency reference to the DMF. As an alternative, you may provide authorization from the holder of the DMF allowing the Agency to access their DMF in support of your application. Please provide the required authorization from the DMF holder.

You have failed to provide a certification of compliance

with current Good Manufacturing Practices/Good Laboratory Practices (cGMP/GLP) from your [redacted] Please provide this certification.

It appears that you have packaged only [redacted] from your ANDA exhibit batch. You are required to completely package your exhibit batch in containers intended for marketing.

[redacted] for which you are not seeking approval is not acceptable unless a protocol has been submitted and approved prior to submission of the application. If, for example, you intend to market your proposed drug product in [redacted] containers, you must provide draft labeling and a side-by-side comparison of your [redacted] labels as well. Please refer to the letters to the industry from the Director, Office of Generic Drugs, dated November 8, 1991, and August 4, 1993. We also refer you to the Office of Generic Drugs' Policy and Procedure Guide #41-95, dated February 8, 1995.

Also, you have failed to provide three additional separately bound copies of your methods of validations. Please provide these copies in **separate** binders.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3). If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

Gregory S. Davis
Project Manager
(301) 827-5862

Sincerely yours.

/S/ 8/13/99

Doug Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research

nephron
pharmaceuticals
corporation
SINCE 1937

JUL 0 2 1999

RTF 8/10/99 ISL

Office of Generic Drugs (HFD-600)
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

REFERENCE: ANDA for Albuterol Sulfate Inhalation Solution, 0.5%

Gentlemen:

Attached, please find our Abbreviated New Drug Application for the production of Albuterol Sulfate Inhalation Solution, 0.5%, as outlined below.

1. PURPOSE OF THE SUBMISSION: To gain approval from the Food and Drug Administration for the production of albuterol sulfate inhalation solution, 0.5% at Nephron's current facility in Orlando, Florida. The proposed drug product is an orally administered bronchodilator, in sterile form, in a unit-of-use 1 mL, (0.5mL fill) [redacted] container, packaged 30 vials to a foil pouch.

   The unit-of-use container nomenclature used in this application is supported by correspondence from OGD/CDER dated April 19, 1999. A copy of the correspondence from Mr. Douglas Sporn's office is attached.

   The facility, equipment, and processes used to manufacture this product are the same as those used to manufacture albuterol sulfate inhalation solution 0.083% previously approved under ANDA 74-880 on September 17, 1997. The facility received a satisfactory GMP inspection from the Orlando District Office in August, 1997.

   The active ingredient (albuterol sulfate) and [redacted] is the same active ingredient and supplier previously approved under ANDA 74-880. The container component [redacted], is the same component and supplier previously approved under ANDA 74-880. The analytical method of analysis is the same as that approved under ANDA 74-880 with the exception of the analyte concentration which is 0.5%.

2. TYPE OF SUBMISSION: This submission is an Abbreviated New Drug Application.

3. PROPRIETARY NAME: None. The generic drug name will be used.

4. NUMBER OF VOLUMES SUBMITTED: 1 Archive Copy, containing 2 volumes
   1 Review Copy, containing 2 volumes
   1 Field Submission Copy, containing 2 volumes
   (submitted to the Orlando District)

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUL 0 6 1999
OGD

4121 34th Street Orlando, FL 32811 (407) 246-1389

5. THIRD COPY CERTIFICATION STATEMENT: We certify that the third (field) copy of this Abbreviated New Drug Application contains a true copy of all sections, both administrative and technical and has been sent directly to the Orlando District Office.

6. Rx / OTC DRUG STATEMENT: This application is for the production of a prescription drug product (Rx).

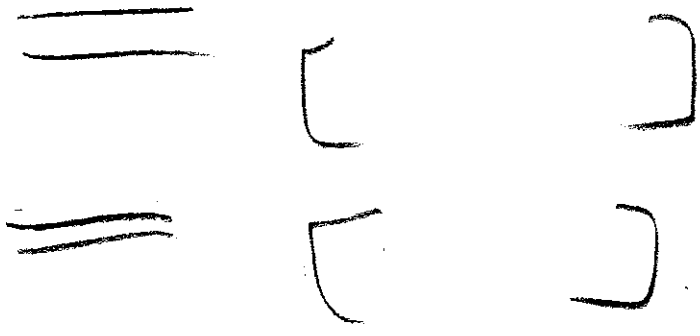
7. FACILITY PERSONNEL: The following Nephron Pharmaceuticals Corporation personnel are available to answer questions concerning this submission:

Administration:	Steven F. Simmons, President
Quality Assurance:	J. Brian Lundberg, Director of Quality Assurance
Quality Control:	Angel Pérez, Manager - Quality Control, Chemistry
	Karen Pendleton, Manager - Quality Control, Microbiology
Production:	Raúl Lugo, Manager - Production

8. CONSULTANTS: The following consultants are authorized to act on behalf of Nephron Pharmaceuticals Corporation concerning this ANDA, in the following capacities:

Outside Counsel:

David L. Rosen, R.Ph., J.D.
Attorney at Law
McDermott, Will & Emery
600 13th St, N.W.
Washington, DC 20005-3096
(202) 756-8075



We appreciate the agency's expedient review of our application, and look forward to an early reply.

Sincerely,

NEPHRON PHARMACEUTICALS CORP.

Steven F. Simmons
President

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Nephron Pharmaceuticals Corporation
Attention: Steven F. Simmons
4121 34th Street
Orlando, FL 32811

APR 19 1999

Reference Number: OGD 99-024

Dear Mr. Simmons:

This letter is in response to your correspondence dated January 13, 1999. You request that the Office of Generic Drugs (OGD) provide further comments regarding packaging of concentrated inhalation solution drug products in unit-dose or single-unit containers. The Office of Generic Drugs has reviewed your new proposal and continues to agree with Nephron that a sterile product is preferred for inhalation solutions. However, your proposal to place concentrated solutions of albuterol sulfate, isoetharine, and metaproterenol sulfate, which require subsequent dilution, into single-unit (unit-dose) containers still remains objectionable for the following reasons:

1. Please note that United States Pharmacopoeia , Twenty-Third Revision (USP), defines two types of single-unit containers; single-dose containers for injections, and unit-dose containers for all other dosage forms. Your proposal remains the same as stated in your October 24, 1997, letter. The proposed packaging configuration is in a single-unit container and, since it is not a parenteral product, would have to meet the USP definition of a unit-dose container.

   > "a unit-dose container is a **single-unit container** for articles intended for administration by other than the parenteral route as a single dose, direct from the container." [Emphasis added]

Since concentrated solutions require further dilution, they cannot be administered directly to the patient upon removal from the container. Therefore, the proposal to place concentrated solutions in unit-dose containers does not meet the USP definition and is unacceptable.

2. Your proposal provides an example of Albuterol Sulfate Inhalation Solution which you contend is packaged and labeled to meet the requirements of **unit-dose** containers. This proposal would not be acceptable for the reasons stated above. However, the packaging of concentrated solutions could be acceptable in **unit-of-use** containers, provided each container meets the requirements of section 502(f) of the Federal Food, Drug, and Cosmetic Act regarding "adequate directions for use". These requirements are codified in 21 CFR 201.5 and 201.100, and can be met by individually packaging each unit (vial, ampule, etc.) with complete labeling. Such a packaging configuration would help to assure the safe use of these products by providing complete instructions for their dosage and administration. Currently

the unit-of-use packaging configuration remains the only configuration acceptable to OGD for the marketing of individual units of concentrated inhalation solutions.

We suggest that you revise your proposal to provide for unit-of use rather than unit-dose packaging.

If you have any questions, please call Ms. Cecelia Parise, R.Ph., Special Assistant to the Director at (301) 827-5845. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

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