CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-949

Clinical Pharmacology and Biopharmaceutics Review

Jun.

MAY - 9 2000

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-949
Albuterol Sulfate 0.042 and 0.021%
Inhalation Solution for Nebulization

SUBMISSION DATE:
12/03/99

BRAND NAME: AccuNeb

SPONSOR: Dey Laboratories

REVIEWER: Tien-Mien Chen, Ph.D.

TYPE OF SUBMISSION: Resubmission to Respond to the Agency's 03/30/99 Action Letter

BACKGROUND:

Albuterol is a β-adrenergic agonist which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (cyclic-AMP) from adenosine triphosphate (ATP). The cyclic-AMP then initiates a series of intracellular events, resulting in physiological responses such as increases in cardiac rate and force of contraction (β_1) and relaxation of bronchial and vascular smooth muscle (β_2).

Previously, Dey's generic albuterol sulfate Inhalation Solution 0.083% was approved under ANDA 72-652 on 02/21/92 for adults and children 12 years of age and older. It is indicated for the relief of bronchospasm in patients with reversible obstructive airway disease and acute attacks of bronchospasm. The recommended dosing regimen is one unit dose (3 ml) given TID or QID.

On 03/27/98, Dey Laboratories filed an original NDA 20-949 for AccuNeb (albuterol sulfate) Inhalation Solution, 0.042% and 0.021%. The sponsor is seeking approval for the same indication as the approved 0.083% albuterol sulfate inhalation solution. The recommended maintenance dosing regimen is one unit dose (3 ml of 0.042% or 0.021%) TID and QID by nebulization for children 2-12 years old.

Submitted under NDA 20-949 were one pivotal clinical trial, No. DL-019, and two human pharmacodynamic (PD) studies, Nos. DL-009 and DL-010 in pediatrics 6-12 years old. No PK data were obtained from the above two PD studies. The above two PD studies had been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE II). The NDA was deemed approvable by the Agency in the 03/30/99 action letter and the Agency's comments were also communicated to the sponsor.

SYNOPSIS:

On 12/03/99, the sponsor submitted their responses including the revised package insert (PI) to the Agency. OCPB has comments on PI revision only. Therefore, the sponsor's revised PI is reviewed here.

RECOMMENDATION:

Dey Laboratories' revised PI that was submitted on 12/03/99 to respond to the Agency's 03/30/99 action letter has been reviewed by OCPB/DPE II. OCPB is of the opinion that the revised PI is acceptable provided that the following changes are incorporated in the PI.

LABELING COMMENT: (Needs to be sent to the sponsor)

Please see the Agency's version of PI revision in Attachment 1 for details.

/S/

05/09/2000

04/29/2000

Tien-Mien Chen, Ph.D.
Division of Pharmaceutical Evaluation II

RD initialed by Ramana. Uppoor, Ph.D. /S/ 05/08/2000

FT initialed by Ramana. Uppoor, Ph.D. /S/ 05/09/2000

cc: NDA 20-949, HFD-570 (Sullivan, Jani), HFD-870 (S.M. Huang, R. Uppoor, T.M. Chen), CDR (B. Murphy).

NDA 20-949 (AccuNeb; Albuterol Sulfate 0.042% and 0.021% Inhalation Solutions)

ATTACHMENT 1

Sponsor's Revised Package Insert (December 1999 Version)

15 pages redacted from this section of the approval package consisted of draft labeling

MAR 1 9 1999

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-949
Albuterol Sulfate 0.042 and 0.021%
Inhalation Solution for Nebulization

SUBMISSION DATE:
03/27/98
05/18/98
07/17/98

BRAND NAME:
Accuneb

SPONSOR: Dey Laboratories

REVIEWER: Tien-Mien Chen, Ph.D.

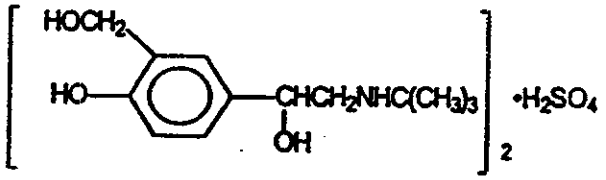
TYPE OF SUBMISSION: Original NDA

Code: 5S

TITLE: "Review of Human Pharmacokinetics and Bioavailability Section of An NDA"

BACKGROUND:

Albuterol sulfate has a chemical formula of $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$ and a molecular weight of 576.7. It is a white or practically white powder, freely soluble in water and slightly soluble in alcohol and its structure is shown below:



Albuterol is a β-adrenergic agonist which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (cyclic-AMP) from adenosine triphosphate (ATP). The cyclic-AMP then initiates a series of intracellular events, resulting in physiological responses such as increases in cardiac rate and force of contraction (β_1) and relaxation of bronchial and vascular smooth muscle (β_2). Albuterol is reportedly highly selective for β_2 and causes relaxation of the smooth muscles of the bronchi, uterus, and vascular supply to the skeletal muscles and inhibition of the release of immediate hypersensitivity mediators from cells (especially mast cells).

Previously, Dey's generic albuterol sulfate Inhalation Solution 0.083% was approved under ANDA 72-652 on 02/21/92 for adults and children 12 years of age and older. It is indicated for the relief of bronchospasm in patients with reversible obstructive airway disease and acute attacks of bronchospasm. The recommended dosing regimen is one unit dose (3 ml) given TID or QID. As indicated by the sponsor, albuterol sulfate has been used in Europe for 20 years and in the US for more than 10 years.

SYNOPSIS:

On 03/27/98, Dey Laboratories filed an original NDA 20-949 for ——— (albuterol sulfate) Inhalation Solution, 0.042% and 0.021%. The sponsor is seeking approval for the same indication as the approved 0.083% albuterol sulfate inhalation solution. The recommended maintenance dosing regimen is one unit dose (3 ml of 0.042% or 0.021%) TID and QID by nebulization for children 2-12 years old. The name, ——— was later changed to Accuneb. Each ml of Accuneb 0.042% contains 0.42 mg of albuterol base (as 0.5 mg of albuterol sulfate) and each ml of Accuneb 0.021% contains 0.21 mg of albuterol base (as 0.25 mg of albuterol sulfate) in an isotonic, sterile, aqueous solution without sulfiting agent. It is supplied in 3 ml unit-dose vials for total doses of 1.25 mg and 0.62 mg albuterol base, respectively. Sulfuric acid is used to adjust the pH between 3 and 5.

Submitted under NDA 20-949 were one pivotal clinical trial, No. DL-019, and two human pharmacodynamic (PD) studies, Nos. DL-009 and DL-010 in pediatrics 6-12 years old. No PK data were obtained from the above two PD studies. To support the PK of Accuneb Inhalation Solution, 0.042% and 0.021%, in children, published articles were submitted Therefore, the two PD studies, DL-009 and DL-010, plus the published articles submitted are reviewed here by the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE II).

A. SUMMARY OF PUBLISHED ARTICLES:

1. PHARMACOKINETICS IN ADULT VOLUNTEERS AND IN PATIENTS:

The PK of albuterol and its metabolite, sulfate conjugate, were investigated in a 2x2 crossover study with a washout period of one week in adults, i.e., **1)** an intravenous (IV) loading dose (400 µg over 5 min) followed by a maintenance infusion (10 µg/min) for 2 hr and **2)** oral administration of 4 mg TID albuterol tablet doses (4 doses). Ten healthy volunteers (5M+5F) were employed (Morgan et al; Br. J. Clin. Pharmacol. 1986, 22: 587). The mean PK results are shown below:

Table1: IV Administration of Albuterol Sulfate in 10 Healthy Adults

IV PK Parameters	CL_{tot}[1] (ml/min)	$T_{1/2}$[2] (hr)	Vd[3] (liter)	Ae_{0-48}[4] (% of dose)	CL_r[5] (ml/min)	$Ae_{0-48,\ sulfate\ conjugate}$[6] (% of dose)
Mean ± SD[7]	480 ± 123	3.9 ± 0.8	156 ± 38	64.2 ± 7.1	291 ± 70	12.0 ± 3.1

1. Total plasma clearance (CL_{tot}) for parent drug, unless specified otherwise.
2. Terminal half-life ($T_{1/2}$).
3. Volume of distribution (Vd).
4. Amount of dose (in %) excreted unchanged in 0-48 hr urine (Ae_{0-48}).
5. Renal clearance of parent drug (CL_r).
6. Amount of dose (in %) excreted as metabolite ($Ae_{0-48,\ sulfate\ conjugate}$).
7. Mean ± standard deviation (SD), unless specified otherwise.

Table2: Oral Administration of Albuterol Tablets in 10 Healthy Adults

Oral PK Parameters	F_{abs} [1]	CL_{cr} [2] (ml/min)	$Ae_{0\text{-}8}$ (% of dose)	CL_r (ml/min)	$Ae_{0\text{-}8,\ sulfate\ conjugate}$ (% of dose)	$Cl_{r,\ met}$ [3] (ml/min)
Mean ± SD	0.50 ± 0.04	118 ± 21	31.8 ± 1.9	272 ± 38	48.2 ± 7.3	98.5 ± 23.5

1. Absolute bioavailability (F_{abs}) calculated as AUC_{oral}/AUC_{iv} (normalized) for parent drug, specified otherwise.
2. Creatinine clearance (CL_{cr}).
3. Renal clearance for sulfate conjugate metabolite ($Cl_{r,\ met}$).

The above results show that **1)** after IV administration, albuterol was largely (≈2/3) excreted unchanged in urine, **2)** the mean CL_{tot} for parent drug was estimated to be 480 ml/min and that for CL_r was 291 ml/min (indicating active tubular secretion), **3)** after oral administration, the peak plasma level (C_{max}) ranged from 10.0 to 16.9 ng/ml and the time to peak (T_{max}) occurred at 1.0 to 4.0 hr, **4)** the mean F_{abs} of oral albuterol doses was estimated to be around 0.50, **5)** albuterol was metabolized mainly to sulfate conjugate due to the first-pass effect (presumably in the intestine as well as in the liver), **6)** mean metabolite AUC was much higher than that of parent drug after oral administration, and **7)** *in vitro* protein binding and blood/plasma ratio for albuterol were reported to be around 7 to 8% and 0.96 ± 0.13, respectively.

Another PK study in 16 healthy volunteers showed that **1)** mean PK parameters obtained from a 5-min IV infusion (1.5 mg) were consistent with the above study, e.g., mean Cl_{tot} being 471 ± 19 ml/min and mean $T_{1/2}$ being 4.0 ± 0.1 hr, **2)** the mean F_{abs} values for single 4 mg oral doses of albuterol liquid, tablet and capsule were also consistent (around 0.43 to 0.44), and **3)** the C_{max} following oral administration ranged from 12.7 to 13.0 ng/ml and the T_{max} occurred 1.7 to 2.2 hr (Goldstein et al; Eur. J. Clin. Pharmacol. 1987, 32: 631).

Data obtained from additional PK study following administration of 4 mg oral syrup and 400 µg MDI of albuterol to 10 healthy volunteers showed that the urinary recovery of parent drug (25.0% vs. 23.9%) and of total dose (63.3 vs. 57.4%) [parent + metabolite] are comparable after oral and inhaled administration (Hindle et al; Br. J. Clin. Pharmacol. 1992, 34: 311).

The deposition of radiolabeled single doses of 0.4 mg albuterol (MDI, DPI, and solution for nebulization) was investigated in 9 adult patients (3M+6F). Technetium-99m labeled Teflon particles mixed with drug preparations were used and images were obtained from a gamma counter (Zainudin et al; Thorax. 1990, 45: 469). The results including PD data for albuterol are shown below:

Table 3: Baseline Lung Function Values and Percentage Total and Peripheral Lung Deposition of Radioaerosol with Improvement in Lung Function Values

	MDI	DPI	Nebulizer
Baseline PEF[2] (L/min)	246 (25)[1]	248 (27)	246 (28)
FEV_1[3] (L)	1.40 (0.13)	1.42 (0.13)	1.43 (015)
FVC[4] (L)	2.25 (0.19)	2.28 (0.18)	2.19 (0.18)
Radioaerosol deposition			
Total lung (%)	11.2 (0.8)	9.1 (0.6)	9.9 (0.7)
Peripheral lung (%) of Total	16.1 (1.2)	12.7 (1.3)	24.5 (1.0)
Improvement (%)			
PEF	40.1 (6.6)	32.4 (6.7)	29.9 (5.2)
FEV_1	35.6 (7.4)	25.2 (6.2)	25.8 (6.5)
FVC	25.4 (4.4)	19.7 (5.3)	24.4 (6.0)

1. Mean (stand error of the mean).
2. Peak expiratory flow (PEF).
3. Forced expiratory volume in one second (FEV_1).
4. Forced vital capacity (FVC).

The above data showed that **1)** around 9-11% of the dose is deposited in the total lungs, **2)** nebulizer had significantly higher fraction of drug particles deposited into the peripheral lungs than the others, and **3)** PEF and FEV_1 were improved significantly after MDI administration than the other two.

Another investigator retrospectively determined albuterol plasma levels after nebulization of solution (0.150 mg/kg) and after a 10-min IV infusion (0.005 mg/kg) in 12 patients (6M+6F) with stable asthma. The results showed that **1)** more pronounced hemodynamic effects after IV administration than nebulization were seen due to higher initial plasma albuterol levels in IV group and **2)** mean C_{max} after nebulization was found to be 6.86 (± 4.92) ng/ml and mean T_{max} occurred at 0.79 (± 0.47) hr (Jason; Eur. Respir. J. 1991, 4: 544).

2. PEDIATRICS:

Systemic absorption of albuterol following nebulized therapy was studied in 35 pediatric patients with acute asthma (19M+16F; age range 1.33-14.5 with a mean of 7.38 ± 4.04 years old). Depending on severity of acute asthma, a one-hr or two-hr dosing regimen was employed.

Table 4. Demographics

	Age		Sex		Dosing Regimen	
Asthma Severity	**5 yr**	**> 5 yr**	**Male**	**Female**	**1 hr**	**2 hr**
Mild	11	9	14	6	3	17
Moderate/Severe	4	11	5	10	9	6

Table 5. Albuterol Levels According to Severity of Asthma and Age Group

		Age Group		Student's t-test
Parameter	**Asthma Severity**	≤5 yr	>5 yr	p-value
Dose administered (µg/kg)	Mild	177.9 (81.0)[1]	144.7 (34.7)	0.268
	Moderate/Severe	181.3 (73.8)	131.9 (23.3)	0.059
Pre-nebulizer (ng/ml)	Mild	11.3 (5.0)	22.2 (9.2)	**0.004***
	Moderate/Severe	9.2 (6.5)	27.0 (11.3)	**0.011***
Post-nebulizer[2] (ng/ml)	Mild	15.0 (6.4)	26.3 (10.0)	**0.006***
	Moderate/Severe	13.1 (6.2)	30.9 (11.2)	**0.011***
Absolute change in plasma levels (ng/ml)	Mild	3.7 (2.5)	4.2 (1.8)	0.627
	Moderate/Severe	4.0 (3.1)	3.9 (1.6)	0.926
% change in plasma levels	Mild	34.3 (20.4)	20.8 (10.6)	0.086
	Moderate/Severe	64.7 (42.8)	16.6 (9.0)	**0.002***
Fraction apparently absorbed[3]	Mild	0.107 (0.04)	0.164 (0.05)	**0.009***
	Moderate/Severe	0.075 (0.03)	0.162 (0/05)	**0.010***

1. Mean (SD).
2. Plasma samples obtained 20 min post dosing.
3. From PK modeling/simulation.
*. Statistically significant between age groups ($p<0.05$).

The author concluded that **1)** for both mild and moderate/severe ratings, the older age group had significantly higher pre-nebulizer baseline values relative to the younger group **(Row 2)**, **2)** the absolute changes in the plasma levels were similar in the two asthma severity groups **(Row 4)**, **3)** the severity of the asthma did not influence the plasma concentrations of salbutamol **(Row 4)**, and **4)** by modeling/simulation of PK data, the estimated fraction of the albuterol dose apparently absorbed by the older group was statistically significantly greater than that of the younger group **(Row 6)** which might be due to a greater clearance of salbutamol by the ≤ 5 year group and/or a greater difficulty using the nebulizer by this group (Penna et al; Acta. Pediatr. 1993, 82: 963).

3. SPECIAL POPULATIONS:

Renal Impairment:
The PK results after an IV dose (10 µg/kg) administered to 5 patients with renal function impairment showed that as compared to healthy subjects, **1)** the Cl_{tot} was lower (167 ± 80 ml/min) and **2)** $T_{1/2}$ was similar (4.27 ± 3.03 hr) indicating a decrease in Vd (55 ± 33 liters; Rey et al; Eur. J. Clin. Pharmcol. 1989, 37: 387).

Cystic Fibrosis:
Nebulized albuterol in solution (mean: 90.0 µg/kg) given to 10 adolescents with cystic fibrosis (CF) and to 5 healthy young adults (82.6 µg/kg) and IV albuterol

(29.2 μg/kg) to 5 other young adult volunteers were studied. The results show that **1)** patients with CF had significantly higher (3.8 fold) AUC value than healthy volunteers and shorter T_{max} (15 to 30 min). The reason is not known. Finally, the mean Cl_{tot} obtained from volunteers (476 ± 22 ml/min) was consistent with those reported previously (Vaisman et al; J. Pediatr. 1987, 119: 914).

Premature Labor:
The PK of IV and oral albuterol given to 9 pregnant women to prevent premature labor was also studied. The results showed that the PK parameters were also consistent with data reported previously for healthy volunteers (Hutchings et al; Br. J. Clin. Pharmacol. 1987, 24: 69).

7. PHARMACODYNAMICS (PD) IN CHILDREN:

A prospective PK study for high (0.15 mg/kg) and low (0.05 mg/kg) doses of nebulized albuterol (every 20 min for 6 doses) was conducted in 32 children (21M+ 11F, aged from 5 to 17 years old) who were treated at the emergency room of a hospital for severe asthma. The results showed that **1)** albuterol mean pre-treatment serum levels were 1.0 ± 2.4 ng/ml and 2.5 ± 4.6 ng/ml for high- and low-dose groups ($p>0.05$), **2)** mean FEV_1 were 29.3 and 32.4% of expected values during the entry at hospital ($p>0.05$), **3)** mean albuterol serum levels at 15 min post-last treatment were reported to be 19.8 ± 10.7 ng/ml and 12.4 ± 6.5 ng/ml ($p<0.05$), **4)** treatment for the low dose, mean % increase in FEV_1 was 58% from baseline and 9.6% from the 1st treatment, and **5)** as compared to the low-dose group, the high-dose had 132% increase from baseline and 34.5% from the 1st treatment ($p<0.05$). The sponsor concluded that much higher doses had significantly better results than the low-dose but no correlations were found between the high albuterol doses and its side effects, e.g., heart rates, vomiting, tremor, etc. ($P>0.05$; Schuh et al; Pediatrics, 1989, 83: 513).

NOTE: It was indicated by the MO that the above study was conducted in children who were admitted to the emergency room for treating severe or acute asthma and the bronchodilator effects of higher dose were distinguishable from low dose probably because these patients had much lower FEV_1 values at entry.

8. DRUG-DRUG (D-D) INTERACTION:

Only a few D-D interaction studies have been reported for albuterol. They are summarized below:

Synthetic beta agonists:

Twenty patients undergoing routine coronary angiography were enrolled in this study. Ten patients treated with atenolol (50-100 mg daily) were compared with

10 patients not treated with β-blockers. It was concluded that the concomitant use of atenolol and albuterol made the heart more sensitive to the positive chronotropic effects of albuterol by intracoronary administration (Hall et al: Circ. Res. 1991, 69: 959).

Dextromethorphan (DMTP):

A double-blind crossover study was done with 10 healthy volunteers to compare the bioavailability of DMTP from a DMTP-albuterol combination tablet (an European Redol comp®) to a plain DMTP tablet (an European Extusion®). The absorption of DMTP from the combination tablet was almost equal to that of DMTP alone. The authors concluded that this combination can be administered in tablet form for the treatment of cough without adjustment of the individual doses (Silvasti et al; Int. J. Clin. Pharmcol. Ther. Toxicol. 1990, 28: 268).

Sulphamethoxazole:

As reported by the author, there was 50% decrease in the absorption rate of sulphamethoxazole in the presence of albuterol and it was quite in agreement with the well known change of gastrointestinal motility by adrenoreceptor agonists. These effects were however, neutralized by an increase in bioavailability (extent of absorption) (Adebayo et al; Eur. J. Drug Metab. Pharmacokinet. 1989, 14: 57).

Digoxin:

A prospective, controlled study to evaluate the effects of IV albuterol on the PK of digoxin in humans was conducted. Ten healthy men were digitalized with digoxin (0.5 mg daily) and, approximately 10 days later, were given an IV injection of either 4 µg/kg albuterol or saline. Albuterol was shown to cause a decrease in the steady state serum digoxin levels but the digoxin levels in skeletal muscle were not significantly changed by albuterol. (Edner et al; Eur. J. Clin. Pharmacol., 1989, 36: 235).

9. FORMULATIONS, DOSAGE, AND DRUG ADMINISTRATION:

It is difficult to verify which formulation (name and strength) was used in the above articles, since most of the time, the above information on formulation/ composition was not clearly given. For the pivotal clinical trial and two human PD studies submitted in this NDA, the formulations and the manufacturing procedures of the 0.042% and 0.021% inhalation solutions employed are the same as the to-be-marketed and the batches tested were manufactured at >10% of the expected commercial batch size.

10. ASSAY:

Various assay methods were used in the above articles for analyzing the albuterol serum levels. The methods, however, could not be verified. No

albuterol serum/plasma levels were obtained from the clinical trial and the two human PD studies submitted under this NDA.

B. TWO PD STUDIES CONDUCTED BY THE SPONSOR:

1. CONSULT REVIEW FOR ALBUTEROL PD DATA ANALYSES:

The PD data obtained from Study Nos. DL-009 and DL-010 were analyzed by Drs. Michael Fossler and Raymond Miller. Please see the consult review in Attachment 1 for details.

Study No. DL-009 was a placebo-controlled, double-blind, single-dose, dose-ranging (0, 0.75, 1.5, and 3 mg), 4 x 4 crossover study of albuterol sulfate using a bronchodilation design. Thirty pediatric patients (18M+12F) with a mean age of 9.4 years old (range 6-12) were enrolled and 28 completed the study. A washout period of 3-9 days was employed. The PD data were analyzed using NONMEM for area under the curve of the value of forced expiratory volume in one second (AUC_{FEV1}) from time zero (dosing) to 6 hr post dosing. The sigmoidal E_{max} model was used. Covariates (weight, BSA, height) were tested for their effects on the model. Upon the request by the reviewing medical officer, additional analyses for the onset and duration of action of the treatments were performed using nonparametric sign test. The non-compartmental parameters were also analyzed using General Linear Model (GLM) procedure of SAS.

The results of the above analyses are summarized below:

1. A significant placebo effect was noted, as $\Delta AUC_{placebo}$ for FEV1 is significantly greater than zero (subtracting $AUC_{baseline}$ from $AUC_{placebo}$).
2. The covariates (weight, BSA, or height) were found <u>not</u> to have a significant impact (except for statistical significance on $ED_{50, AUC}$ for FEV_1).
3. The ED_{50} (the dose required to produce 50% of $E_{max, AUC}$) was estimated to be around 0.69 mg albuterol sulfate which is close to the dose of 0.75 mg albuterol sulfate (equivalent to 3 ml of Accuneb 0.021%; 0.62 mg albuterol).
4. The onset of action for all 4 treatments (0.083 hr or 5 min) does <u>not</u> differ significantly from one another.
5. The duration of effect for the 1.5 and 3 mg treatment arms (4-6 hr) is significantly greater than placebo, while that for the 0.75 mg approaches statistical significance.
6. Using different approaches of analysis, albuterol shows a measurable pharmacological effect.

Study No. DL-010 was a placebo-controlled, double-blind, single-dose, dose-ranging (0, 0.75, 1.5, and 3 mg), 4 x 4 crossover study of albuterol sulfate using a bronchoprovocation design. Twenty-five pediatric patients (15M+10F) with a mean age of 10.0 years old (range 6-12) were enrolled and 24 completed the study. A washout period of 3-9 days was employed. Two methacholine

challenges by inhalation were given on the treatment day. The first challenge was given at pre-treatment baseline and then the second one (3 hr apart) starting at 15 min post-treatment of albuterol inhalation solution. Methacholine dose was given exponentially. The concentration of methacholine that caused a 20% reduction in FEV1 (PC_{20}) was determined otherwise the test was stopped when the maximum dose of methacholine (128 mg/ml) was given. Comparison of PC_{20} values among the 4 treatments was done using GLM.

The results of the above analyses are summarized below:

1. All treatments showed significant improvement over placebo because ED_{50} values are significantly greater than zero, but the dose response curve was very flat.
2. Attempting to determine a dose-response relationship between the PC_{20} and albuterol dose was problematic because the PC_{20} in 17 (out of 98) measurements was truncated since the maximum dose of methacholine was reached before a reduction in 20% of FEV1 was achieved.
3. Based on the results obtained, an albuterol sulfate dose of 1.0 to 1.5 mg is recommended for the study in a larger patient population.

GENERAL COMMENTS: (Need not be sent to the sponsor)

1. The results of NONMEM analysis on PD data obtained from Study No. DL-009 showed that weight, BSA, or height each had significant influence on the estimate of $ED_{50, AUC}$ (for FEV_1). The sponsor indicated that the above analysis implied that as the size of the child increases, the $ED_{50, AUC}$ decreases (i.e., less drug is required to achieve a given effect). Upon discussion with the reviewing MO, he indicated that **1)** the pivotal clinical trial No. DL-019 showed opposite relationship, i.e., heavier children may require a higher fixed dose and **2)** sponsor reanalyzed study No. DL-009. The reanalysis indicated that the scatterplots of the AUC_{FEV1} vs. age and weight showed no discernable trends. Therefore, the implication/interpretation that smaller children require higher dose of albuterol sulfate is not confirmed.

2. Ventolin (albuterol sulfate) 0.5% and 0.083% inhalation solutions for nebulization have been approved for pediatric patients 2 to 12 years old. For this NDA, the sponsor is also seeking approval for Accuneb 0.042% and 0.021% for pediatric patients 2-12 years old, but only recruited pediatric patients 6-12 years old in the PD studies as well as in the pivotal clinical trial. Therefore, there were no PK and/or PD studies to support the age group between 2 to 6 years old.

RECOMMENDATION:

NDA 20-949 (albuterol sulfate inhalation solution) that was filed on 03/27/97 by Dey has been reviewed by OCPB/DPE II. OCPB is of the opinion that the NDA is considered to be acceptable from OCPB's perspective and the reviewing medical division should

make the final decision on the age range to be recommended for this product. The following labeling comments, as appropriate, need to be conveyed to the sponsor.

LABELING COMMENTS: (Need to be sent to the sponsor)

The following changes (underlined) are recommended;

1. Under "CLINICAL PHARMACOLOGY":

[redacted]

PHARMACODYNAMICS:

[redacted]

2. Under "INDICATIONS AND USAGE":

[ ] is indicated for the relief of bronchospasm in [ ] with asthma (reversible obstructive airway disease) [ ]

3. Under "PRECAUTIONS":

Drug Interactions: — sympathomimetic aerosol bronchodilators or epinephrine should not be used concomitantly with . —

— t should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, —

—

Beta-receptor blocking agents —

Pediatric Use: Safety and effectiveness of — have been established in pediatric patients between the ages of x and 12 years."

4. Under "DOSAGE AND ADMINISTRATION":

The maintenance dosage for patients x to 12 years old is —
of . — administered 3 or 4 times daily — . More frequent administration is not recommended.
To administer 1.25 mg or — mg of albuterol —, use the entire contents of one unit-dose vial (3 mL of — by nebulization. —

—

The use of . — can be continued as medically indicated to control recurring bouts of bronchospasm. During this time most patients gain optimum benefit from regular use of the inhalation 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.

CPB Briefing on 03/16/99: Drs. M.L. Chen, R Uppoor, M. Fossler, S. Kim, and D. O'Hearn (MO)

/S/ 02/28/99
Tien-Mien Chen, Ph.D.
Division of Pharmaceutical Evaluation II

RD initialed by Ramana Uppoor, Ph.D. RU 03/03/99
FT initialed by Ramana Uppoor, Ph.D. /S/ 03/18/99

cc: NDA 20-949, HFD-570 (O'Hearn, Hilfiker), HFD-870 (M.L. Chen, R. Uppoor, T.M. Chen, M. Fossler), HFD-850 (R. Miller), CDR (B. Murphy).

NDA 20-949 (Accuneb; Albuterol Sulfate 0.042% and 0.021% Inhalation Solutions)

ATTACHMENT 1

A Consult Review by Drs. Michael Fossler and Raymond Miller

Pharmacometrics Consult

NDA:	20-949
Albuterol Sulfate Solutions for Inhalation (0.042 and 0.021%)	
Original Submission Date:	27 March 1998
Sponsor:	Dey Laboratories
Type of Submission:	Original New Drug Application
Primary Reviewer:	Albert Chen
Medical Division:	HFD-570
Reviewer:	Michael J. Fossler Raymond Miller

Submission

The submission dated 3/27/98 is a New Drug Application for [redacted] (albuterol solution for inhalation), indicated for [redacted] The submission consists of three studies, two of which were studies in pediatric patients utilizing non-linear mixed-effect modeling. At the request of the primary reviewer, these studies were reviewed by the Pharmacometrics group.

Study 1: DL-009: A placebo-controlled, double-blind, dose-ranging study of albuterol sulfate using a bronchodilation design in pediatric patients with asthma.

Study Design

Randomized, double-blind, placebo-controlled, four-way crossover study. Thirty pediatric patients with asthma were randomized to receive each of the following doses: 0, 0.75 mg, 1.5 mg, or 3.0 mg albuterol. After dosing, the FEV1 of each subject was measured at 0 (pre-dose). 5, 15, and 30 minutes, and 1, 1.5, 2, 3, 4, 5, and 6 hours post-dose.

Data Analysis

NONMEM version 5 was used for the analysis. For each patient/treatment, the AUC of the FEV1 measurements were computed. The overall AUC data were modeled as:

$$AUC = AUC_{baseline} + AUC_{placebo} + AUC_{drug} + \varepsilon$$

where $AUC_{baseline}$ is the observed value of the pre-dose response multiplied by the duration of the study (6 hours), $AUC_{placebo}$ is the change in AUC due to placebo, and AUC_{drug} is the change in AUC due to the drug. The term ε is an error term representing residual error.

The model for AUC_{drug} is based on the Hill equation as follows:

$$AUC_{drug} = \frac{E_{max,AUC} D^{\gamma}}{D^{\gamma} + D_{50,AUC}^{\gamma}}$$

where $E_{max,AUC}$ is the maximum AUC_{drug}, D is the dose, D_{50} is the dose that produces ½ $E_{max,AUC}$, and γ is a shape factor which controls the slope of the line. Covariates (weight, BSA, height)

were also tested for their effects on the model, but were found not to have a significant impact. The coding for the final NONMEM run (annotated by the reviewer) is included in the Appendix.

At the request of the reviewing medical officer, some additional analyses were carried out. These included the following:

- Estimation of onset and duration of action - this was performed by the reviewer by defining onset as the first of two consecutive points that were ≥15% over baseline. Duration of action was taken as the difference between onset and offset of action (defined as the first of two consecutive points that fell below the onset value).
- Non-compartmental analyses including AUC $_{FEV1}$, FEV1$_{max}$ (maximum FEV1 reached over the 6 hours), t $_{max}$ (time post-dose the maximum was reached), and FEV1$_{ave}$ (the average FEV1 over the 6 hr interval, computed as the AUC $_{FEV1}$/6.

The onset and duration data were analyzed using the nonparametric sign test. The non-compartmental parameters were analyzed using the General Linear Models procedure of SAS version 6.12.

Results

NONMEM Analysis

Table 1 shows the results of the NONMEM analysis. A significant placebo effect is noted in the study, as AUC $_{placebo}$ is significantly greater than zero. The dose required to produce 50% of the maximum effect (0.69 mg) is very close to the minimum recommended dose in the labeling (0.62 mg), although this parameter is not especially well-estimated.

Table 1: Parameter estimates (and 95% confidence intervals for AUC $_{FEV1}$) n=23 for all.

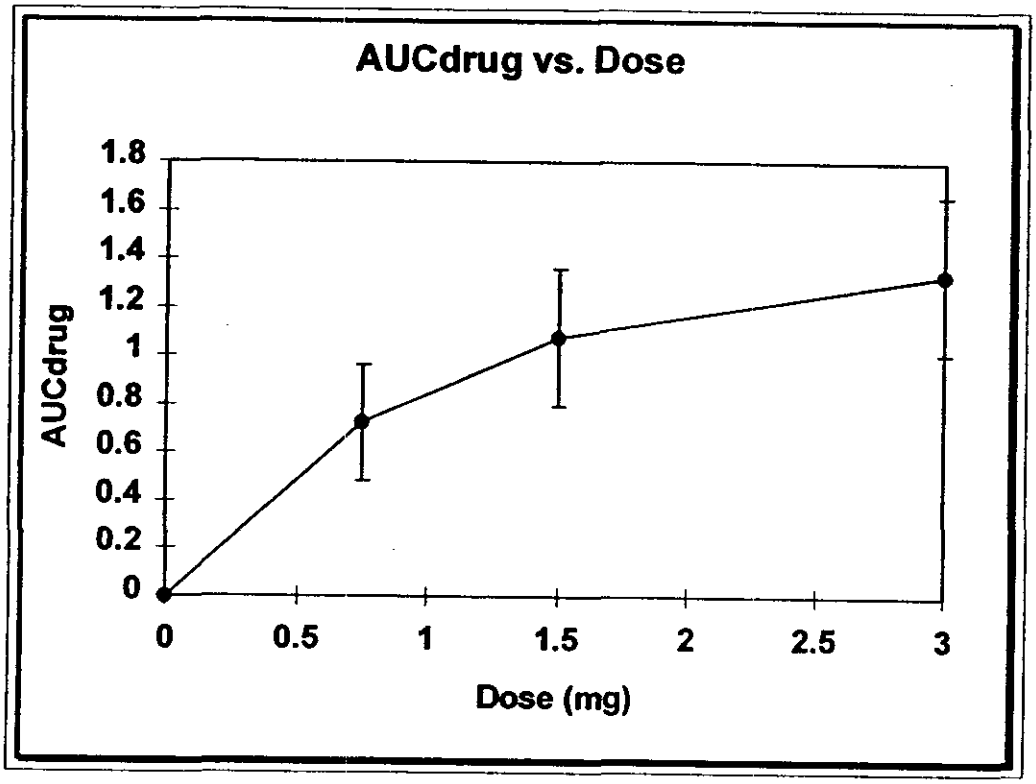
Parameter	Mean (95% CI)
AUC $_{placebo}$	1.12 (0.71, 1.71)
E $_{max\ AUC}$	1.30 (0.80, 1.80)
D_{50}	0.69 (0.28, 1.10)
γ	1.85 (0.59, 3.11)

Using the model, it was possible to estimate the AUC$_{drug}$ for each subject/treatment. The reviewer performed this analysis; the results are shown in Table 2 and Figure 1. From Figure 1, it can be noted that each treatment has a significant effect over placebo; however, there is considerable overlap between the active treatment arms.

Table 2: AUC$_{drug}$ for each treatment.

Dose	Mean (95% CI)
placebo	0 (n.a.)
0.75 mg	0.72 (0.48, 0.96)
1.5 mg	1.08 (0.79, 1.36)
3 mg	1.33 (1.00, 1.66)

Figure 1: AUC_{drug} as a function of dose. Mean ± 2 SE shown.



Onset, Duration of Action

These data are shown in Table 3. The onset of action for all four treatments do not differ significantly from one another; however, the duration of effect for the 1.5 and 3 mg treatment arms is significantly greater than placebo. The comparison between placebo and the 0.75 mg treatment approaches statistical significance. Overall, these data support the preceding analysis and clearly indicate that albuterol is having a measurable pharmacological effect.

Table 3: Onset, duration of action for the four treatments.

	Placebo		0.75 mg		1.5 mg		3 mg	
	Onset	Duration	Onset	Duration	Onset	Duration	Onset	Duration
Median	0.083	1	0.083	4	0.083	6	0.083	4
Min	[							]
Max	[							]
p-value	na	na	0.2256	0.0537	0.1934	0.0016	0.2256	0.0097

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Noncompartmental Analyses

The data are summarized in Table 4. These results are in basic agreement with the preceding analyses, in that they clearly show that abuterol at all doses is having a pharmacological (albeit modest) effect as compared with placebo.

The results of this analysis are in reasonable agreement with the NONMEM analysis. For example, from Table 4, comparing the AUC_{FEV1} between 1.5 mg and placebo, the increase that may be attributable to drug is about 1.2 L/hr. This estimates compares well with the estimate from NONMEM (1.08). Thus, the two approaches may be considered equivalent.

Table 4: Results of non-compartmental analysis of FEV1 data.

	Mean ± SD			
Dose	AUC_{FEV1}	$FEV1_{ave}$	$FEV1_{max}$	t_{max}
placebo	10.8 ± 3.2	1.8 ± 0.5	1.9 ± 0.5	2.0 (0.1, 6.0)
0.75 mg	11.6 ± 3.5	1.9 ± 0.6	2.1 ± 0.6	1.0 (0.1, 5.0)
1.5 mg	12.0 ± 3.6	2.0 ± 0.6	2.2 ± 0.6	1.5 (0.1, 6.0)
3.0 mg	12.2 ± 3.8	2.0 ± 0.6	2.2 ± 0.7	1.0 (0.1, 4.0)
Pairwise comparisons (95% CI of the least-square mean ratios)				
0.75 mg vs. placebo	112 (108, 116)	112 (108, 116)	113 (108, 118)	na
1.5 mg vs. placebo	110 (106, 114)	110 (106, 114)	112 (107, 117)	na
3.0 mg vs. placebo	107 (103, 111)	107 (103, 111)	109 (104, 113)	na

Conclusions

1) At all doses studied, albuterol administered as [redacted] solution for inhalation demonstrates a measurable pharmacologic effect over placebo.
2) The results from both the NONMEM analysis and the non-compartmental analysis are similar, suggesting that the two approaches may be considered equivalent.

Study 2: DL-010/UCSF#DAD94-04A placebo-controlled double-blind dose-ranging study of albuterol sulfate, using a bronchoprovocation design, in pediatric patients with asthma.

Study Design

The objective of this study was to establish a dose-response relationship of albuterol sulfate when administered as a nebulized treatment for asthma in children ages 6 through 12 years.

The study was a double-blind, randomized 4-way crossover trial consisting of a single dose of 0 (placebo), 0.75, 1.5, and 3 mg albuterol sulfate given by nebulizer. Treatments were separated by 3-9 days. FEV_1 was the effect measured. Metacholine challenge tests were performed before study treatment and after study treatment during each visit. Metacholine was administered in exponentially increasing doses until FEV_1 decreased at least 20% relative to pre-baseline or pre-treatment or until the highest metacholine dose, 128 mg/ml was administered. The dose of metacholine which decreased FEV_1 by 20%, or the maximum dose (128 mg/ml) was recorded as PC_{20}. Twenty-five children between the ages of 6 and 12 years with moderately severe asthma were evaluated.

Data Analysis and Results

To evaluate efficacy of albuterol in the dose range studied, comparison of PC_{20} values among the 4 treatment groups was made with the use of a General Linear Model (GLM) procedure and Waller Duncan K-ratio T test (SAS version 6.08). For this comparison all data was used as is. All treatments showed significant improvement over placebo.
An attempt to elucidate a dose response relationship with this same data proved to be unsuccessful in that a flat dose reponse relationship was determined. In the original data there were 17 PC_{20} values (out of 98) in eight subjects (all during the treatment phase) associated with metacholine challenge that exceeded the highest metacholine dose (128 mg/ml). The ceiling dose, and thus truncated PC_{20} values was thought to have blunted the differentiation between doses. This deficiency was corrected by fitting the metacholine-time data to a polynomial function using nonlinear mixed effect modeling (NONMEM) and extrapolating the metacholine dose to the PC_{20} beyond 128 mg/ml. In this case fitting an E_{max} model to the data resulted in a reasonable estimate of D_{50}, the dose that produces 50% of the maximal response (0.87 mg (95% confidence interval 0.76, 1.0 mg)) and E_{max} (62.8 mg/ml (95% confidence interval 37.1, 106 mg)). Efficacy is concluded based on the fact that D_{50} is significantly greater than zero (Chi square).

Conclusion

Albuterol doses of 0.75, 1.5 and 3.0 mg when administered to asthmatic children from 6 to 12 years show clinical benefit compared to placebo because D_{50} values are significantly greater than zero and because the mean change in PC_{20} (from baseline) with each active treatment differed significantly from that of placebo. Based on the results an albuterol dose of 1.0 to 1.5 mg is recommended for study in a larger patient population.

Reviewer's Comment

The clinical benefit of Albuterol in this group of children is demonstrated by the fact that the observed PC_{20} values are significantly different for all the doses compared to placebo using GLM. Attempting to demonstrate a dose-response relationship was problematic because the PC_{20} in a number of cases was truncated due to the fact that the maximum metacholine dose was reached before a reduction in 20% in the FEV_1 was achieved. The fact that all of these truncated PC_{20} values were reached in patients on active treatment is supportive evidence that Albuterol is effective at the doses administered. The use of extrapolated PC_{20} values in these patients allowed a reasonable estimate of the dose-response relationship and provides useful information regarding possible doses to be used in further studies i.e. 1.0 to 1.5 mg.

/S/ 12/15/98

/Michael J. Fossler, Pharm.D., Ph.D.

/S/ 12/15/98

Raymond Miller, D.Sc.

Pharmacometrics Branch
Office of Clinical Pharmacology and Biopharmaceutics

CC: NDA 20-949(orig., 1 copy), HFD-850(Lesko, Ray Miller), HFD-870(M.Chen, Fossler,)
Version: Final

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page(s) of trade secret and/or confidential commercial information (b4)

NDA 20-949 (Accuneb; Albuterol Sulfate 0.042% and 0.021% Inhalation Solutions)

ATTACHMENT 2

Sponsor's Proposed Package Insert (March 98 Version)

10 pages redacted from this section of the approval package consisted of draft labeling