

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20950

CHEMISTRY REVIEW(S)

Division of Pulmonary Drug Products

MAY 19 1999

Review of Chemistry, Manufacturing and Controls

Hilfiker

NDA #: 20-950

CHEM. REVIEW #: 1 **REVIEW DATE:** May 17, 1999

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original	28-MAY-98	29-MAY-98	04-JUN-98
Amendment [BC]	02-JUL-98	06-JUL-98	09-JUL-98
Amendment [BC]	26-MAR-99	30-MAR-99	31-MAR-99

*Subjects of this review.

NAME AND ADDRESS OF APPLICANT:

Attn: Ms. Peggy J. Berry
Regulatory Affairs Manager
Dey Laboratories
2751 Napa Valley Corporate Drive
Napa, CA 94558

DRUG PRODUCT NAME:

Proprietary:

Duoneb™

Nonproprietary/USAN:

Combination Albuterol Sulfate and Ipratropium Bromide Inhalation Solution

Code Name/#:

CAS Registry # 51022-70-9 and #66985-17-9

Chem. Type/Ther. Class:

3S

Established Name of Drug Substance:

α^1 -[(tert-butylamino)methyl]-4-hydroxy-m-xylene- α, α' -diol sulfate (2:1) (salt) and 8-azoniabicyclo[3.2.1]-octane, 3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-, bromide, monohydrate (endo, syn) - (\pm)

PHARMACOL. CATEGORY/INDICATION:

Treatment of bronchospasm associated with COPD in patients requiring more than one bronchodilator.

DOSAGE FORM:

Inhalation solution

STRENGTHS: Each 3 mL vial of Duoneb™ contains 2.5 mg (0.083%) of albuterol (3.0 mg of albuterol sulfate) and 0.5 mg (0.017%) of ipratropium bromide. The sterile solution is provided in a 3 mL LDPE vials. Cards of five vials are placed into a laminated overwrap pouch. One, five, six, or twelve pouches are packaged in a shelf carton.

ROUTE OF ADMINISTRATION:

Oral Inhalation

Rx/OTC:

Prescription

NDA 20-950 (Duoneb)

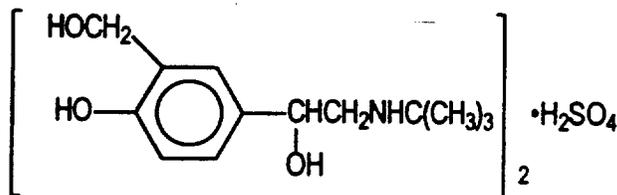
page 2

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR WEIGHT:

The chemical name of albuterol sulfate is α' -[(*tert*-butylamino)methyl]-4-hydroxy-*m*-xylene- α , α' -diol sulfate (2:1) (salt). Other chemical names are as follows: 1-(4-hydroxy-3-hydroxymethylphenyl)-2-(*tert*-butylamino)ethanol sulfate ; 1,3-Benzene-dimethanol α' 1-[[[(1,1-dimethylethyl)amino]methyl]-4-hydroxy-sulfate (2:1) (salt) (\pm)2-Hemisulfate of 1-(4-hydroxy-3-hydroxymethylphenyl)-2-(*tert*-butylamino) ethanol

The Chemical Abstract Service (CAS) registry number is 51022-70-9.

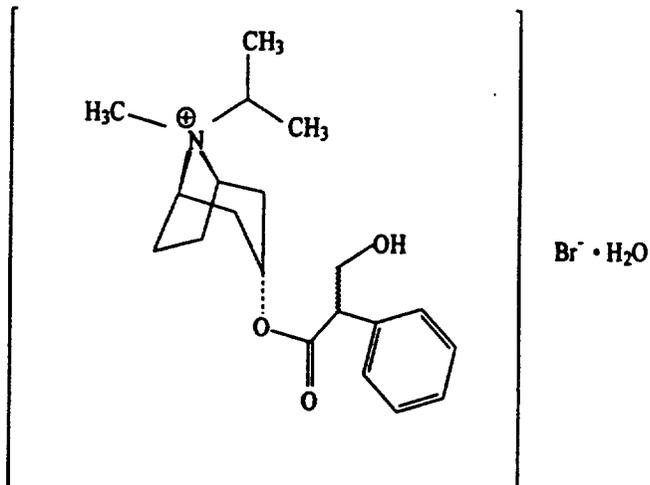
Other names for albuterol sulfate are albuterol hemisulfate, salbutamol sulfate, and salbutamol hemisulfate.



The chemical name of ipratropium bromide is 8-azoniabicyclo[3.2.1]octane, 3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-, bromide, monohydrate (*endo,syn*)-, (\pm). Other chemical names are as follows:

(8 γ)-3 α -hydroxy-8-isopropyl-1- α H, 5 α H-tropanium bromide (\pm) tropate, monohydrate; (1R3r.5S.8r)-3-[(RS)-(3-hydroxy-2-phenylpropionyl)-oxy]-8-isopropyl-8-methyl-azabicyclo[3.2.1]octane bromide monohydrate

The CAS registry number is 66985-17-9.



SUPPORTING DOCUMENTS:

DMFs

NDA 20-950 (Duoneb)

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REMARKS/COMMENTS:

1. Methods validation by the Agency should be deferred pending resolution of deficiencies in the methods as requested.
2. Many pending CMC issues related to albuterol sulfate, container and closure system, which are also applicable to this NDA were raised in the first review of NDA 20-949 (Accuneb; albuterol sulfate inhalation solution). Those issues are directly cited onto this NDA.

CONCLUSION AND RECOMMENDATION:

The NDA is not approvable from CMC standpoints. Deficiencies should be conveyed to the applicant.

Chong-Ho Kim
Chong-Ho Kim, Ph.D.
Review Chemist, HFD-570

cc: Orig. NDA #20-950
HFD-570 Division File
HFD-570/CHKim
HFD-570/GPoochikian
HFD-570/RAnthracite
HFD-570/VWhitehurst
HFD-570/DHilfiker
R/D Init. by: *APG/1/19/23*
doc: NDA 20950r1.401

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Manufacturing Controls

JUN 1 2000

Division of Pulmonary and Allergy Drug Products
Review of Chemistry, Manufacturing and Controls

NDA #: 20-950 CHEM. REVIEW #: 2 REVIEW DATE: June 1, 2000

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original	28-MAY-98	29-MAY-98	04-JUN-98
Amendment [BC]	02-JUL-98	06-JUL-98	09-JUL-98
Amendment [BC]	26-MAR-99	30-MAR-99	31-MAR-99
Amendment [AZ]*	29-NOV-99	02-DEC-99	02-DEC-99
Amendment [BC]*	20-JAN-00	21-JAN-00	22-JAN-00

*Subjects of this review.

NAME AND ADDRESS OF APPLICANT:
Attn: Ms. Peggy J. Berry
Regulatory Affairs Manager
Dey Laboratories
2751 Napa Valley Corporate Drive
Napa, CA 94558

DRUG PRODUCT NAME:

Proprietary: Duoneb™ Inhalation Solution

Nonproprietary/USAN: Combination Albuterol Sulfate and Ipratropium Bromide Inhalation Solution

Code Name/#: CAS Registry # 51022-70-9 and #66985-17-9

Chem. Type/Ther. Class: 3S

Established Name of Drug Substance:

α¹-[(tert-butylamino)methyl]-4-hydroxy-*m*-xylene-α,α'-diol sulfate(2:1) (salt) and 8-azoniabicyclo[3.2.1]-octane, 3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-, bromide, monohydrate (endo, syn) - (±)

PHARMACOL. CATEGORY/INDICATION: Treatment of bronchospasm associated with COPD in patients requiring more than one bronchodilator.

DOSAGE FORM: Inhalation solution

STRENGTHS: Each 3 mL vial of Duoneb™ contains 2.5 mg (0.083%) of albuterol (3.0 mg of albuterol sulfate) and 0.5 mg (0.017%) of ipratropium bromide. The sterile solution is provided in a 3 mL LDPE vials. Cards of five vials are placed into a laminated overwrap pouch. One, five, six, or twelve pouches are packaged in a shelf carton.

ROUTE OF ADMINISTRATION: Oral Inhalation

Rx/OTC: Prescription

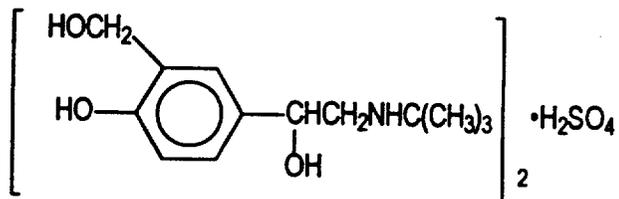
Special Product: No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR WEIGHT:

The chemical name of albuterol sulfate is α^1 -[(*tert*-butylamino)methyl]-4-hydroxy-*m*-xylene- α , α' -diol sulfate (2:1) (salt). Other chemical names are as follows: 1-(4-hydroxy-3-hydroxymethylphenyl)-2-(*tert*-butylamino)ethanol sulfate ; 1,3-Benzene-dimethanol α^1 -[[1,1-dimethylethyl)amino]methyl]-4-hydroxy-sulfate (2:1) (salt) (\pm)2-Hemisulfate of 1-(4-hydroxy-3-hydroxymethylphenyl)-2-(*tert*-butylamino) ethanol

The Chemical Abstract Service (CAS) registry number is 51022-70-9.

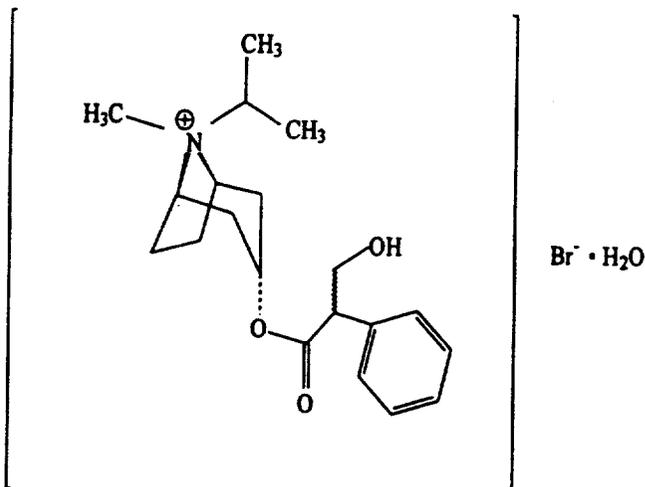
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The chemical name of ipratropium bromide is 8-azoniabicyclo[3.2.1]octane, 3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-, bromide, monohydrate (*endo,syn*)-, (\pm). Other chemical names are as follows:

(8 γ)-3 α -hydroxy-8-isopropyl-1- α H, 5 α H-tropanium bromide (\pm) tropate, monohydrate; (1R3r.5S.8r)-3-[(RS)-(3-hydroxy-2-phenylpropionyl)-oxy]-8-isopropyl-8-methyl-azabicyclo[3.2.1]octane bromide monohydrate

The CAS registry number is 66985-17-9.



SUPPORTING DOCUMENTS:

DMFs

# & Type	Holder	Subject	Date Reviewed	Status
		Albuterol Sulfate	4/30/00 by Dr. Shah	Adequate
		Ipratropium Bromide	7/17/98 by Dr. Schwartz	Adequate
		Manufacture of overwrap pouch foil laminate TRP74027	Chem Rev. #2, NDA 20-949	Inadequate
		Rexene Polyethylene Resin	Chem Rev. #2, NDA 20-949	Adequate
		Manufacture of MP-710 rubber-based adhesive	Chem Rev. #2, NDA 20-949	Inadequate
		Water based printing ink products	Chem Rev. #2, NDA 20-949	Inadequate

RELATED DOCUMENTS:

IND Albuterol Sulfate and Ipratropium Bromide Inhalation Solution.

CROSS REFERENCES:

NDA 20-228: Ipratropium Bromide Inhalation Solution 0.02%/mL (Atrovent); Boehringer Ingelheim; approved 9/93.

NDA 19-243: Albuterol Sulfate Inhalation Solution; equivalent to 0.083% of albuterol base (Proventil); Schering; approved 1/87.

NDA 19-269: Albuterol Sulfate Inhalation Solution; equivalent to 0.5% of albuterol base (Ventolin); Glaxo Wellcome; approved 1/87.

NDA 19-773: Albuterol Sulfate Inhalation Solution; equivalent to 0.083% of albuterol base (Ventolin); Glaxo Wellcome; approved 4/92.

CONSULTS:

1. Labeling and Nomenclature Committee ruled that the proposed trade name (Duovent) was not acceptable (9/3/98). The applicant has proposed a new name "Duoneb" which was reviewed by OPDRA. OPDRA has no objection to the use of the name "DuoNeb" (4/17/00).
2. Applicant has submitted a categorical exclusion based on the fact that the estimated concentration of the drug substance at the point of entry into the aquatic environment will be below 1 ppb. (Acceptable)
3. FUR is acceptable (May 18, 2000).
4. Biometrics consult: Applicant proposes 18 month expiration dating period with 24 months stability data. A biometrics consult is not necessary for this application.
5. Microbiology consult; Microbiology staff recommends approval of this

submission. (Review dated May 10, 2000)

REMARKS/COMMENTS:

1. We would request new copies of method validation package once we have agreement on methods.
2. Comments pertain to the drug substance, albuterol sulfate, in the Chemistry Review #2 of NDA 20-949 (albuterol sulfate inhalation solution) are equally applicable to this NDA.
3. Comments pertain to the container and closure system in the Chemistry Review #2 of NDA 20-949 (albuterol sulfate inhalation solution) are equally applicable to this NDA.

CONCLUSION AND RECOMMENDATION:

The NDA is not approvable from CMC standpoints. Deficiencies should be conveyed to the applicant.



Chong-Ho Kim, Ph.D.
Review Chemist, HFD-570

cc: Orig. NDA #20-950
HFD-570 Division File
HFD-570/CHKim
HFD-570/GPoochikian
HFD-570/RAnthracite
HFD-570/VWhitehurst
HFD-570/DHilfiker
R/D Init. by: *GR 6/1/00*
doc: NDA 20950r2f.601

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Manufacturing Controls

Division of Pulmonary and Allergy Drug Products
Review of Chemistry, Manufacturing and Controls

NDA #: 20-950

CHEM. REVIEW #: 3 **REVIEW DATE:** March 20, 2001

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original	28-MAY-98	29-MAY-98	04-JUN-98
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Amendment [BC]	26-MAR-99	30-MAR-99	31-MAR-99
Amendment [AZ]	29-NOV-99	02-DEC-99	02-DEC-99
Amendment [BC]	20-JAN-00	21-JAN-00	22-JAN-00
Amendment [AZ]*	19-SEP-00	22-SEP-00	26-SEP-00
Amendment [BC]*	23-OCT-00	25-OCT-00	26-OCT-00
Amendment [BL]*	06-DEC-00	08-DEC-00	12-DEC-00
Amendment [BC]*	12-DEC-00	14-DEC-00	18-DEC-00
Amendment [BL]*	14-FEB-01	15-FEB-01	21-FEB-01
Amendment [BL]*	15-FEB-01	20-FEB-00	21-FEB-01
Amendment [BC]*	22-FEB-01	26-FEB-01	05-MAR-01
Amendment [BC]*	27-FEB-01	01-MAR-01	01-MAR-01
Amendment [BC]*	28-FEB-01	01-MAR-01	01-MAR-01
Amendment [BC]*	01-MAR-01	01-MAR-01	01-MAR-01
Amendment [BC]*	06-MAR-01	02-MAR-01	02-MAR-01
Amendment [BZ]*	09-MAR-01	07-MAR-01	07-MAR-01
Amendment [BC]*	12-MAR-01	13-MAR-01	13-MAR-01
Amendment [BC]*	15-MAR-01	14-MAR-01	14-MAR-01
Amendment [BZ]*	15-MAR-01	16-MAR-01	16-MAR-01
Amendment [BL]*	15-MAR-01	16-MAR-01	16-MAR-01
Amendment [BL]*	16-MAR-01	16-MAR-01	16-MAR-01
Amendment [BC]*	19-MAR-01	19-MAR-01	19-MAR-01
Amendment [BC]*	19-MAR-01	20-MAR-01	20-MAR-01

*Subjects of this review.

NAME AND ADDRESS OF APPLICANT:

Attn: Ms. Peggy J. Berry
 Regulatory Affairs Manager
 Dey Laboratories
 2751 Napa Valley Corporate Drive
 Napa, CA 94558

DRUG PRODUCT NAME:

Proprietary:

DuoNeb™ Inhalation Solution

Nonproprietary/USAN:

Albuterol Sulfate and Ipratropium Bromide
 Inhalation Solution

Code Name/#:

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 (salt) and 8-azoniabicyclo[3.2.1]-octane, 3-(3-hydroxy-1-oxo-2-
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 endo, *syn*) - (±)

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NDA 20-950

Review #3

Page 2

overwrap pouch. One, five, six, or twelve pouches are packaged in a shelf carton.

ROUTE OF ADMINISTRATION: Oral Inhalation

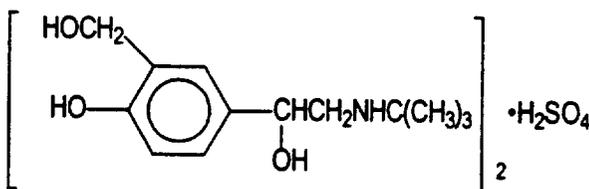
Rx/OTC: Prescription

Special Product: No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR WEIGHT:

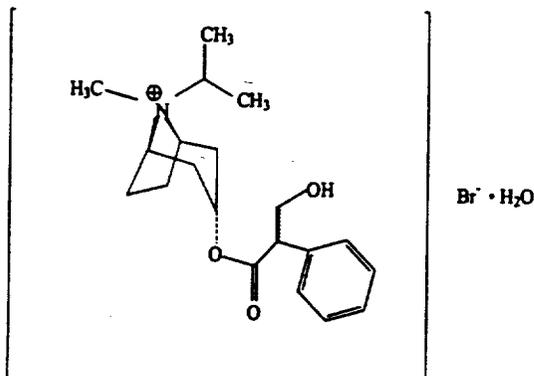
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The Chemical Abstract Service (CAS) registry number is 51022-70-9. Other names for albuterol sulfate are albuterol hemisulfate, salbutamol sulfate, and salbutamol hemisulfate.



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The CAS registry number is 66985-17-9.



SUPPORTING DOCUMENTS:

DMFs# & Type	Holder	Subject	Date Reviewed	Status
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		Ipratropium Bromide	7/17/98 by Dr. Schwartz	Adequate
		Manufacture of overwrap pouch foil laminate	Chem Rev. #2, NDA 20-949	*Inadequate
		overwrap	Dr. Liu (2/1/00) & Dr. Shah (3/25/99)	Adequate**
		Polyethylene Resin	Chem Rev. #2, NDA 20-949	Adequate
		Manufacture of rubber-based adhesive	Chem Rev. #2, NDA 20-949	*Inadequate
		Water based printing ink products	Chem Rev. #2, NDA 20-949	*Inadequate

*DMFs

were withdrawn from the current application.

**Dr Shah reviewed the DMF in regard to NDA 20-837 (Levalbuterol.HCl Inhalation Solution) on March 25, 1999. Dr. Liu reviewed the DMF for ANDA 75-437 (Cromolyn Sodium Inhalation Solution, USP) and found it adequate. I concur with their reviews.

RELATED DOCUMENTS:

IND [] Albuterol Sulfate and Ipratropium Bromide Inhalation Solution.

CROSS REFERENCES:

NDA 20-228: Ipratropium Bromide Inhalation Solution 0.02%/mL (Atrovent); Boehringer Ingelheim; approved 9/93.

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2. Applicant has submitted a categorical exclusion based on the fact that the estimated concentration of the drug substance at the point of entry into the aquatic environment will be below 1 ppb. (Acceptable)

NDA 20-950

Review #3

Page 4

3. FUR is acceptable. (March 05, 2001)
4. Biometrics consult: Applicant proposes 18 month expiration dating period with 24 months stability data. A biometrics consult is not necessary for this application.
5. Microbiology consult; Microbiology staff recommends approval of this submission. (Review dated May 10, 2000)
6. Pharm/Tox consult stated that the proposed specifications for [] and extractables are acceptable. The applicant has agreed to conduct a 90 day inhalation toxicity study to qualify [] as a phase 4 commitment. (Consult Review dated February 20, 2001)

REMARKS/COMMENTS:

1. Updated method validation packages were provided. Method validation was requested on March 20, 2001.
2. Applicant has replaced the overwrap pouch source from [(DMF [] to [(DMF []]
3. Applicant has decided to emboss the LDPE vials; comments 5 through 8 do not need to be addressed. Applicant should provide a sample of LDPE vial as soon as available.

CONCLUSION AND RECOMMENDATION:

The NDA is approvable from CMC standpoints. Project manager should include "list of commitments" in the approval letter.

Chong-Ho Kim, Ph.D.
Review Chemist, HFD-570

cc: Orig. NDA #20-950
HFD-570 Division File
HFD-570/CHKim
HFD-570/GPoochikian
HFD-570/RAnthracite
HFD-570/VWhitehurst
HFD-570/DHilfiker
R/D Init. by:

doc: NDA 20950r3.m20

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manufacturing Controls