

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-949

Microbiology Review(s)

MAY 10 2000

REVIEW FOR HFD-570
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #2 OF NDAs

May 9, 2000

- A. 1. NDA 20-949
20-950
- APPLICANT Dey Laboratories
Napa, California
2. PRODUCT NAMES: AccuNeb (NDA 20-949)
3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: Sterile inhalation solutions without preservatives, in mL LDPE vials
4. METHOD(S) OF STERILIZATION:
5. PHARMACOLOGICAL CATEGORY: bronchodilators
6. DRUG PRIORITY CLASSIFICATION: 5S (20-949) and
- B. 1. DATE OF INITIAL SUBMISSION: March 27, 1998 (20-949) and May 28, 1998
2. DATE OF AMENDMENT: 3 December 1999 (20-949), and 29 November 1999
3. RELATED DOCUMENTS: none
4. ASSIGNED FOR REVIEW: January 24, 2000 (Microbiologist's questions), and May 5, 2000 (question 7 from NDA 20-949, 3 December 1999 amendment)
- C. REMARKS: Both applications were similar and contained similar deficiencies. The applicant responds to the same set of deficiency questions, except that the microbiology review of included a comment about a confusing notation in the sterility test method. Lastly, "Question 7" to NDA 20-949 (letter date 30 March 1999) was not

provided from the Microbiology Staff and, based on the nature of the drug substance and process controls, was not an appropriate question.

- D. **CONCLUSIONS:** The submission is recommended for APPROVAL. The applicant should be notified that routine tests for bioburden in the active ingredient may be discontinued.

5-9-2000
David Hussong, Ph.D.
PK 5/10/00

cc:

- Original NDAs 20-949
- HFD 570/Division Files
- HFD 160/Consult File
- HFD 570/CSO/Hilfiker
- HFD 570/Chemist/Kim
- HFD 570/Chemist/Shah
- HFD 805/D. Hussong

Drafted by: D. Hussong, 05/09/2000
R/D initialed by: P. Cooney

Filename, d:\nda\20-949rv2.DOC

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commercial information

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DEC 17 1998

REVIEW FOR HFD-570
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #1 OF NDA

December 8, 1998

- A. 1. **NDA** 20-949
- SPONSOR** Dey Laboratories
 Napa, California
2. **PRODUCT NAMES:** — (Albuterol Sulfate) Inhalation Solution, 0.021% and 0.042%
3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:** Inhalation solution without preservative, in a 3 mL (nominal) LDPE — vial. Vials are in groups of 5, packaged in a — overwrap.
4. **METHOD(S) OF STERILIZATION:** —
5. **PHARMACOLOGICAL CATEGORY:** Smooth muscle relaxant for bronchodilation.
6. **DRUG PRIORITY CLASSIFICATION:** 5S
- B. 1. **DATE OF INITIAL SUBMISSION:** March 27, 1998
2. **DATE OF AMENDMENT:** (n/a)
3. **RELATED DOCUMENTS:** DMF # — for Albuterol Sulfate, the active ingredient. DMF # —, for — to make the vial. DMF # — the overwrap. DMF letters of authorization are provided in Appendix 1, volume 1.2.
4. **ASSIGNED FOR REVIEW:** September 2, 1998

C. **REMARKS:** This is an original NDA submission. The application provides for sterile, preservative-free inhalation solutions. Proposed FDA regulations will require inhalation solution products to be rendered sterile by their process of manufacture.

Volume 1 of the application was not provided for consult review. Volumes 2 through 5 were provided for review. Volume 1.5 contains a section on the product. The applicant, Dey Laboratories, has submitted applications for sterile products previously. These include ANDAs 70-805 and 71-786, both of which are metaproterenol.

D. **CONCLUSIONS:** The submission is approvable. Deficiencies are provided at the end of the review.

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/S/
12-8-98
~~David Hussong, Ph.D.~~
PAC 12/17/98

cc:

- HFD 160/Consult File
- HFD 570/CSO/D. Hilfkar/C Shumaker
- HFD 820/V. Shah/G. Poochikian
- HFD 805/D. Hussong

Drafted by: D. Hussong, 12/08/98

R/D initialed by: P. Cooney

Filename, d:\nda\20-949r1.DOC

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION**

REQUEST FOR CONSULTATION

To: (Division/Office) **Supervisory Microbiologist HFD-160** FROM: **Vibhakar J. Shah, Ph.D. (HFD-820)**

DATE August 21, 1998	IND NO.	NDA NO. 20949	TYPE OF DOCUMENT Original Application	DATE OF DOCUMENT March 27, 1998
NAME OF DRUG (Albuterol sulfate) Inhalation Solution		PRIORITY CONSIDERATION 5	CLASSIFICATION OF DRUG S	DESIRED COMPLETION DATE Team Goal Date October 31, 1998 PDUFA Goal Date March 31, 1999

NAME OF FIRM
2751 Napa Valley Corporate Drive, Napa, CA 94558 Tel: (707) 224-3200 Fax: (707) 224-3235

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> OTHER (Specify below) |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

- | | |
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| STATISTICAL EVALUATION BRANCH | STATISTICAL APPLICATION BRANCH |
| <input type="checkbox"/> TYPE A OR B NDA REVIEW | <input type="checkbox"/> CHEMISTRY |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER |
| <input type="checkbox"/> OTHER | |

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS/SPECIAL INSTRUCTIONS (Attach additional sheets if necessary):

Please evaluate the methods listed on the attached page which pertain to the microbial quality of the drug product, (albuterol sulfate) Inhalation Solution. The product composition (p 038/ v1.02) is provided on the following page with this consult. The product is manufactured as unit dose vial product solution is : by Dey Laboratories. The bulk drug product solution is :

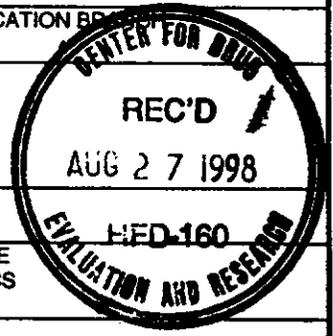
The validation data for the Products (p 037, v1.3) are provided on p 210/v1.5 of the submission.

It should be noted that there is no microbial limit test for the drug substance, albuterol sulfate. The drug substance specifications are on p 27 and the drug product specifications are on pp 61-62 of vol 1.2 of the submission.

CC: Orig. NDA HFD-570 Div. File CSO/DH/ikar Chemist/ VShah Chemistry TL/GPoochikian

SIGNATURE OF REQUESTER _____ METHOD OF DELIVERY (Check one) MAIL HAND

SIGNATURE OF RE _____ SIGNATURE OF DELIVERER _____



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the approval package consisted of draft labeling

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1-11-1999 for 5/4/00

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	REQUEST FOR CONSULTATION
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TO: (Division/Office) Supervisory Microbiologist HFD-160	FROM: Vibhakar J. Shah (HFD-820)
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DATE May 04, 2000	IND NO.	NDA NO. 20949	TYPE OF DOCUMENT Resubmission of NDA	DATE OF DOCUMENT December 03, 1999
NAME OF DRUG Albuterol Sulfate Inhalation Solution		PRIORITY CONSIDERATION 5	CLASSIFICATION OF DRUG S	DESIRED COMPLETION DATE May 15, 2000 PDUFA Due Date June 02, 2000

NAME OF FIRM
 Dey L.P., 2751 Napa Valley Corporate Drive, Napa, CA 94558; Tel: (707) 224-3200; Fax: (707) 224-3235

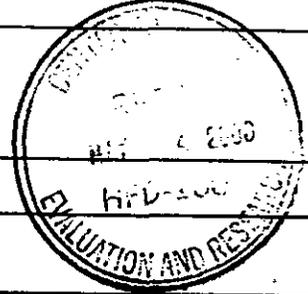
REASON FOR REQUEST

- I. GENERAL**
- | | | |
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| <input type="checkbox"/> NEW PROTOCOL
<input type="checkbox"/> PROGRESS REPORT
<input type="checkbox"/> NEW CORRESPONDENCE
<input type="checkbox"/> DRUG ADVERTISING
<input type="checkbox"/> ADVERSE REACTION REPORT
<input type="checkbox"/> MANUFACTURING CHANGE/ADDITION
<input type="checkbox"/> MEETING PLANNED BY _____ | <input type="checkbox"/> PRE-NDA MEETING
<input type="checkbox"/> END OF PHASE II MEETING
<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> SAFETY/EFFICACY
<input type="checkbox"/> PAPER NDA
<input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER
<input type="checkbox"/> FINAL PRINTED LABELING
<input type="checkbox"/> LABELING REVISION
<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE
<input type="checkbox"/> FORMULATIVE REVIEW
<input type="checkbox"/> OTHER (Specify below) |
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II. BIOMETRICS

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|--|--|
| STATISTICAL EVALUATION BRANCH | STATISTICAL APPLICATION BRANCH |
| <input type="checkbox"/> TYPE A OR B NDA REVIEW
<input type="checkbox"/> END OF PHASE II MEETING
<input type="checkbox"/> CONTROLLED STUDIES
<input type="checkbox"/> PROTOCOL REVIEW
<input type="checkbox"/> OTHER | <input type="checkbox"/> CHEMISTRY
<input type="checkbox"/> PHARMACOLOGY
<input type="checkbox"/> BIOPHARMACEUTICS
<input type="checkbox"/> OTHER |

P: 1/5/00
PK 5/5/00



III. BIOPHARMACEUTICS

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| <input type="checkbox"/> DISSOLUTION
<input type="checkbox"/> BIOAVAILABILITY STUDIES
<input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE
<input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS
<input type="checkbox"/> IN-VIVO WAIVER REQUEST |
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IV. DRUG EXPERIENCE

- | | |
|--|---|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
<input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)
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<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE
<input type="checkbox"/> POISON RISK ANALYSIS |
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V. SCIENTIFIC INVESTIGATIONS

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| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
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COMMENTS/SPECIAL INSTRUCTIONS (Attach additional sheets if necessary):

Please evaluate the microbial limit test method (vol. 5, pp. 0186-0189) and its validation data (vol. 1, pp. 0292-0351), provided for the drug substance albuterol sulfate, in response to comment 7 of Agency's March 30, 1999 AE letter. In spite of Agency's request, applicant has not yet established microbial limit for the drug substance, albuterol sulfate.

CC:
 Orig. NDA HFD-570 Div. File CSO/DHilfiker Chemist/ VShah Chemistry TL/GPoochikian

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
	<input type="checkbox"/> MAIL <input type="checkbox"/> HAND

SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER
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1/5/00
05-04-2000