CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-949

Microbiology Review(s)

Hilfiker

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.

/S/ 5-9-2000

David Hussong, Ph.D.

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

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 [redacted] the product. The applicant, Dey Laboratories, has submitted applications for sterile products [redacted] 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.

/S/ 12-8-98

David Hussong, Ph.D.

RC 12/17/98

cc:

HFD 160/Consult File
HFD 570/CSO/D. Hilfikar/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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page(s) of trade secret and/or confidential commercial information

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

REQUEST FOR CONSULTATIO

/S/ 8/26/98

TO: *(Division/Office)* Supervisory Microbiologist HFD-160

FROM: Vibhakar J. Shah, Ph.D. (HFD-820)

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
August 21, 1998		20949	Original Application	March 27, 1998

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
—— (Albuterol sulfate) Inhalation Solution	5	S	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

/S/ 8/27/98

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW	☐ CHEMISTRY
☐ END OF PHASE II MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☐ OTHER
☐ OTHER	

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
AUG 27 1998
HFD-160

III. BIOPHARMACEUTICS

☐ DISSOLUTION	☐ DEFICIENCY LETTER RESPONSE
☐ BIOAVAILABLITY STUDIES	☐ PROTOCOL-BIOPHARMACEUTICS
☐ PHASE IV STUDIES	☐ *IN-VIVO* WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	☐ SUMMARY OF ADVERSE EXPERIENCE
☐ CASE REPORTS OF SPECIFIC REACTIONS *(List below)*	☐ POISON RISK ANALYSIS
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

/S/ 9-2-98 DH

☐ CLINICAL	☐ 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 ____ 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/DHilfikar /S/

SIGNATURE OF REQUESTER /S/	☒ Chemist/ VShah ☒ Chemistry TL/GPoochikian
	METHOD OF DELIVERY *(Check one)* ☒ MAIL ☐ HAND
SIGNATURE OF RE /S/	SIGNATURE OF DELIVERER

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

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

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 (HFD-820)	
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

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

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER	☐ CHEMISTRY ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER

TO: CSO 5/5/00

III. BIOPHARMACEUTICS

☐ DISSOLUTION ☐ BIOAVAILABLITY STUDIES ☐ PHASE IV STUDIES	☐ DEFICIENCY LETTER RESPONSE ☐ PROTOCOL-BIOPHARMACEUTICS ☐ *IN-VIVO* WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES ☐ CASE REPORTS OF SPECIFIC REACTIONS *(List below)* ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY ☐ SUMMARY OF ADVERSE EXPERIENCE ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

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)* ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER 05-04-2000	SIGNATURE OF DELIVERER

EVALUATION AND RES