CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-949

Administrative/Correspondence

PATENT CERTIFICATION

This certification is provided with respect to the United States Patent and Trademark Office and in compliance with 21 CFR 314.53(b) and 314.53(c)(3) that, in the opinion of the applicant and to the best of its knowledge, there are no patents that claim the drug substance, drug product formulation or composition or method of use for —— (albuterol sulfate inhalation solution 0.021% and 0.042% referred to in this application.

Peggy J. Berry
Regulatory Affairs Project Manager
Dey Laboratories

Date: 3/23/98

EXCLUSIVITY SUMMARY for NDA # 20-949 SUPPL # _____

Trade Name AccuNeb Inh. Soln. Generic Name albuterol sulfate

Applicant Name Dey Laboratories HFD- 570

Approval Date April 30, 2001

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/ X / NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /___/

      If yes, what type(SE1, SE2, etc.)? _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES / X / NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      _____

      _____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /_X_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 19-243 Proventil Inh. Soln.

NDA # 19-773 Ventolin Inh. Soln.

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /_X_/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X_/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # DL-009

Investigation #2, Study # DL-010

Investigation #3, Study # DL-019

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been

relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /_X_/
Investigation #2	YES /___/	NO /_X_/
Investigation #3	YES /___/	NO /_X_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /_X_/
Investigation #2	YES /___/	NO /_X_/
Investigation #3	YES /___/	NO /_X_/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_1_, Study # DL-009

Investigation #_2_, Study # DL-010

Investigation #_3_, Study # DL-019

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 44281 YES /_X_/ NO /___/ Explain: _____

Investigation #2

IND # 44281 YES /_X_/ NO /___/ Explain: _____

Investigation #3

IND # 44281 YES /_X_/ ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

_____

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Marianne Mann
4/30/01 05:22:23 PM
Signing for Dr. Robert J. Meyer, Division Director

FDA Links Searches Check Lists Tracking Links Calendars Reports Help

PEDIATRIC PAGE (Complete for all original application and all efficacy supplements)

View as Word Document

NDA Number:	020949	**Trade Name:**	ACCUNEB INHALATION SOLUTION
Supplement Number:	000	**Generic Name:**	ALBUTEROL SULFATE INHALATION SOLUTION
Supplement Type:	N	**Dosage Form:**	
Regulatory Action:	AE	**COMIS Indication:**	RELIEF OF BRONCHOSPASM IN PATIENTS WITH ASTHMA (REVERSIBLE OBSTRUCTIVE AIRWAY DISEASE)
Action Date:	3/30/99		

Indication # 1 relief of bronchospasm associated with asthma in patients 2-12 years of age

Label Adequacy: Adequate for SOME pediatric age groups

Formulation Needed: NO NEW FORMULATION is needed

Comments (if any): Applicant will need to address the population from birth to 2 years of age to fulfill the Pediatric Rule post-approval.

Ranges for This Indication

Lower Range	Upper Range	Status	Date
0 years	2 years	Deferred	12/31/02
Comments: Albuterol inhalation solutions are used for the acute care of infants with idiological wheezing conditions. The Division has requested that other applicants address all age groups down to birth for other short-acting bronchodilators.			
2 years	12 years	Completed	

This page was last edited on 3/29/01

Signature

4/17/01
Date

DEBARMENT CERTIFICATION

I Certify that neither Dey Laboratories nor any person affiliated with this application has been convicted of any crime described in Sections 306 (a) or (b) of the Generic Drug Enforcement Act of 1992 and Dey Laboratories, has not, does not and will not use the services of any person debarred under sections 306 (a) or (b) for the Generic Drug Enforcement Act of 1992.

Peggy J. Berry

Peggy Berry
Regulatory Affairs Project Manager
Dey Laboratories

Date: 3/23/98

4/30/01

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 20-949 /SE ____ - ____

Drug AccuNeb Inhalation Solution Applicant Dey Laboratories

RPM Hilfiker Phone 301-827-1084

☐505(b)(1)
☑505(b)(2) Reference listed drug Ventolin MDI; generic albuterol sulfate inhalation soln.

☐Fast Track ☐Rolling Review Review priority: ☑ S ☐P

Pivotal IND(s) 44,281

Application classifications:
Chem Class 5S
Other (e.g., orphan, OTC) ____

PDUFA Goal Dates:
Primary April 30, 2001
Secondary same

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- User Fee Information: ☑ User Fee Paid
  ☐ User Fee Waiver (attach waiver notification letter)
  ☐ User Fee Exemption
- Action Letter..... ☑AP ☐ AE ☐NA
- Labeling & Labels
  - Approved labeling and reviews..... Yes
  - Original proposed labeling (package insert, patient package insert) ..... Yes
  - Other labeling in class (most recent 3) or class labeling..... No
  - Has DDMAC reviewed the labeling? ..... ☑ Yes (include review) ☐ No
  - Immediate container and carton labels ..... Yes
  - Nomenclature review ..... Yes
- Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This applieation ☐ is ☑ is not on the AIP.
  - Exception for review (Center Director's memo)..... ____
  - OC Clearance for approval..... ____

Continued ⇨

- Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review) ☐ Materials requested in AP letter

- Post-marketing Commitments — Yes
  - Agency request for Phase 4 Commitments ..... 6-6-00 AE ltr, # 12
  - Copy of Applicant's commitments ..... Yes

- Was Press Office notified of action (for approval action only)? ..... ☐ Yes ☑ No
  - Copy of Press Release or Talk Paper .....

- Patent
  - Information [505(b)(1)] ..... N/A
  - Patent Certification [505(b)(2)] ..... Yes
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)] ..... N/A

- Exclusivity Summary ..... Yes

- Debarment Statement ..... Yes

- Financial Disclosure
  - No disclosable information X
  - Disclosable information – indicate where review is located .....

- Correspondence/Memoranda/Faxes ..... Yes

- Minutes of Meetings ..... Yes
  - Date of EOP2 Meeting _____
  - Date of pre NDA Meeting 8-11-97
  - Date of pre-AP Safety Conference N/A

- Advisory Committee Meeting ..... N/A
  - Date of Meeting .....
  - Questions considered by the committee .....
  - Minutes or 48-hour alert or pertinent section of transcript .....

- Federal Register Notices, DESI documents ..... N/A

CLINICAL INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) ..... Yes

- Clinical review(s) and memoranda ..... Yes

Continued ⇨

- Safety Update review(s) ..... Yes

- Pediatric Information
  ☐ Waiver/partial waiver (Indicate location of rationale for waiver) ☑ Deferred
  Pediatric Page..... Yes
  ☐ Pediatric Exclusivity requested? ☐ Denied ☐ Granted ☑ Not Applicable

- Statistical review(s) and memoranda ..... Yes

- Biopharmaceutical review(s) and memoranda..... Yes

- Abuse Liability review(s) ..... N/A
  Recommendation for scheduling ..... _____

- Microbiology (efficacy) review(s) and memoranda ..... N/A

- DSI Audits ..... Yes
  ☑Clinical studies ☐ bioequivalence studies ..... _____

CMC INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- CMC review(s) and memoranda ..... Yes

- Statistics review(s) and memoranda regarding dissolution and/or stability ..... N/A

- DMF review(s) ..... No

- Environmental Assessment review/FONSI/Categorical exemption ..... See review #1, p. 80 and review #2, p. 102

- Micro (validation of sterilization) review(s) and memoranda ..... Yes

- Facilities Inspection (include EES report)
  Date completed 2-1-01 ..... ☑ Acceptable ☐ Not Acceptable

- Methods Validation ..... ☐ Completed ☑ Not Completed

PRECLINICAL PHARM/TOX INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- Pharm/Tox review(s) and memoranda ..... Yes

- Memo from DSI regarding GLP inspection (if any) ..... N/A

Continued ⇨

- Statistical review(s) of carcinogenicity studies ..... N/A
- CAC/ECAC report ..... N/A

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Marianne Mann
4/30/01 05:18:39 PM
Signing for Dr. Robert J. Meyer, Division Director.

Division Director's Memorandum

Date:	Friday, April 27, 2001
NDA:	20-949
Sponsor:	Dey Laboratories
Proprietary Name:	Accuneb (albuterol sulfate) Inhalation Solution 1.25 mg and 0.63 mg albuterol base/vial

---

Introduction: This is the third review cycle for this NDA that provides for more dilute solutions of albuterol in unit-dose LDPE vials for the treatment of asthma in younger children with bronchospasm. Current racemic albuterol solutions in LDPE vials contain 2.5 mg of albuterol base (as albuterol sulfate). See Dr. Jenkins' original Director's Memo of 3-28-99 for details of the original review. The remaining issues for this cycle were mainly chemistry (including issues related to the over-wrap and vial labeling) and pharm/tox (qualification of drug substance related impurities). The last approvable action was issued on June 6, 2000, and the regulatory due date for this response is April 30th, 2001.

CMC: All of the CMC issues have either been fully resolved, or there are agreements in place sufficient to assure quality at this time with potential revisions to specifications and or methods in the future based on further data. It should be noted that the final labeling of the vials is via —

Pharmacology/toxicology: Since the qualifying toxicology study for the — impurity of albuterol is not completed and reviewed, this study will be made a phase-4 commitment with a date of submission one year hence.

Clinical / Stastical: An safety update was reviewed by Dr. Sullivan and showed no new issues.

Labeling: OPDRA has agreed to ACCUNEB as an appropriate trade name. Although there has been an effort to label content by the drug salt (i.e., for this product albuterol sulfate content), we will label this product for albuterol base content. The reason for this is that this product represents a dosage modification from the standard LDPE vials of albuterol solution for nebulizers (also albuterol sulfate) and those products are currently labeled either as percent solutions or as albuterol base content. The latter is preferable to the former, and for consistency and clarity, will be adopted for this product. Otherwise, satisfactory product and package labeling has been attained.

Conclusions: This NDA will be approved with only one phase-4 commitment for toxicologic qualification of the — mpurity of albuterol.

Robert J. Meyer, MD
Director, Division of Pulmonary and Allergy Drug Products.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Meyer
4/27/01 09:37:05 AM
MEDICAL OFFICER

Memorandum of Telephone Facsimile Correspondence

Date: March 16, 2001

To: Peggy Berry, Dey L.P. Regulatory Affairs

Fax No.: 707-224-1364

From: David Hilfiker
Project Manager

Subject: CMC Comments for AccuNeb

# of Pages: 5

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

Peggy:

The following comments are preliminary and are being provided to you in advance of the completion of our CMC review for NDA 20-949. Your response to these comments is needed to complete our review. Please provide a response to these comments in an electronic file, in addition to your archival medium, if possible.

1. The following comments pertain to the methods that are used for drug substance and the drug product.

   a. Since the method — has been adopted to quantitate impurities and degradation products related to albuterol in the drug product, revise methods [redacted] to delete all the information and references [redacted]

   (*Comment 1c*)

   b. Since method — has been indicated and retained as a stability-indicating method for the assay of albuterol sulfate both in the drug substance and the drug product, remove method — . Alternatively, identify the circumstances that may justify the use of each method. If method — is retained, clarify its objective/purpose with reference to potency assay of "reduced strength" albuterol sulfate inhalation solution, and explain how it is different from method — in determining the potency assay of albuterol sulfate in the drug product. (*Comment 1c*)

2. The proposed specification [redacted] Explain this discrepancy with the proposed specification of [redacted] AccuNeb Inhalation solution [redacted] Provide any information that you may have regarding the [redacted] (Comment 11.b.)

3. As requested earlier (teleconference dated March 06, 2001), address the following comments pertaining to the container closure system.

   a. Provide information on the operation of [redacted] as a part of the method [redacted]

   b. Revise methods [redacted] to include the limit of detection (LOD) and limit of quantitation (LOQ), as appropriate. Resubmit the revised methods, as appropriate. (Comment 3.c.)

c. Express the limit of [ ] Resubmit the revised acceptance specification [ ] accordingly that reflects this change. (Comment 3.c.)

d. Provide [ ] data in [ ] Comment 3.b.(2))

4. Since [ ] has been discontinued and replaced with [ ] for AccuNeb Inhalation Solution, delete all the references and information that are not relevant to [ ] in the acceptance specification [ ] for the foil- [ ] Resubmit the revised acceptance specification [ ] that reflects this change. (Comment 9.b.)

5. Submit the methods validation package in triplicate that reflects the changes indicated in above comments.

6. The following comments pertain to the stability protocols [ ] submitted for both strengths of the drug product (Comment 10).

a. Revise the sampling plan for "Annual Stability Batches" to reflect your commitment made in response to comment 10.b.

b. Revise the "stability commitment" section to incorporate the following statements:

(1) Withdraw from the market any batches found to fall outside the approved specifications for the drug product. If we have any evidence that the deviation is a single occurrence that does not affect the safety and efficacy of the product, we will discuss it with the agency as soon as possible and provide justification for the continued distribution of that batch. The change or deterioration in the distributed drug product will be reported under 21 CFR 314.81(b)(1)(ii) or 21CFR 601.14, respectively.

(2) As appropriate, conduct and/or complete the necessary studies on [ ] production batches and annual batches thereafter of the approved drug product in all container and closure sizes and strengths according to the approved stability protocol through the expiration dating period. (Comment 11.c.)

(3) Submit cumulative stability study results on commitments and annual batches in the annual report, and present the data for each attribute of the

drug product in a format that was requested in our June 6, 2000, approvable letter, in addition to the traditional format of stability data.

c. Correct the inaccurate acceptance criterion indicated for foreign particulate that are greater than in the electronic copies (.xls file) of stability interval report and stability report summary for AccuNeb Inhalation Solution, 0.63 mg/3mL.

d. Provide updated stability protocols that reflect all of the above modifications.

7. The following comments pertain to vial label, overwrap pouch label, carton label, and package insert, as appropriate. These comments are applicable to both strengths of the drug product.

a. The following text is recommended for the content of the vial label. Express Expiration Dating in MM/YY format (e.g., FEB 01) and use appropriate font and font size to maximize the legibility.

Individual Vial Label (	
Vial Front	**Vial Back**
AccuNeb™ 1.50 mg	**Albuterol Sulfate Inhalation Solution, Sterile**
Extended Bottom Front	**Extended Bottom Back**
Expiration Dating	**Lot Number**

b. Express strength (potency) of the drug product in terms of the active pharmaceutical ingredient, albuterol sulfate (e.g., 1.5 mg albuterol sulfate per 3 mL and 0.75 mg albuterol sulfate per 3 mL). Wherever permitted with space on each piece of labeling, you may indicate the amount of albuterol base per 3mL that is equivalent to albuterol sulfate per 3mL with an asterisk.

c. Revise the storage statement as follows:

Protect from light. Store between 2° - 25°C (36°F – 77°F).
Store the Unit-dose vials in the protective foil pouch at all times. Once removed from the foil pouch, use the vial(s) within one week. Discard the vial if the solution is not colorless. Keep out of reach of children.

d. Specify target pH of the solution [ ] wherever it appears.

8. Provide a commitment to perform the following studies or provide the data if you have conducted the following studies.

a. Evaluate the amount of material nebulized under defined in vitro conditions by the proposed nebulizer/compressor system.

b. Evaluate the droplet size distribution of the emitted dose from the nebulizer under the same in vitro conditions.

/s/

David Hilfiker
3/16/01 04:10:59 PM
CSO
receipt confirmed

Electronic Mail Message

Date: 3/9/2001 8:05:55 AM
From: Jerry Phillips (PHILLIPSJ)
To: David Hilfiker (HILFIKERD)
Cc: Sammie Beam (BEAMS)
Subject: Final Clearance AccuNeb ——

David:

Please consider this an official OPDRA response to your 2/27/01 consult request concerning final clearance for AccuNeb and —— proprietary names. OPDRA has previously found these names acceptable and has no objection to the final approval of these proprietary names for NDA's 20-949 —— If you have further questions please contact Sammie Beam. Thanks.

Jerry Phillips
Associate Director, OPDRA

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

REQUEST FOR CONSULTATION

TO (Division/Office): **HFD-400/OPDRA/Associate Director for Medication Error Prevention**			FROM: **HFD-570/DPADP/Hilfiker**	
DATE: February 27, 2001	IDA NO.:	NDA NO.: **20-949**	TYPE OF DOCUMENT: Pre-Approval Confirmation	DATE OF DOCUMENT: N/A
NAME OF DRUG: AccuNeb	PRIORITY CONSIDERATION: rush		CLASSIFICATION OF DRUG: 3S	DESIRED COMPLETION DATE: **March 14, 2001**

NAME OF FIRM: Dey Laboratories

REASON FOR REQUEST

I. GENERAL

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

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 REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER:

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY 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: We may approve these NDA applications within 90 days with the following tradenames:
NDA 20-949, AccuNeb (0.63 and 1.25 mg per 3 mL albuterol sulfate) Inhalation Solution

Please confirm the acceptability of these tradenames by the date indicated above. You may refer to previous tradename reviews dated April 27, 2000 (both NDAs).

SIGNATURE OF REQUESTER: (Hilfiker)	METHOD OF DELIVERY (Check one): ☒ MAIL ☐ HAND
SIGNATURE OF RECEIVER:	SIGNATURE OF DELIVERER:

/s/

David Hilfiker
2/27/01 04:24:13 PM
Potential approval within 90 days

Memorandum

To: NDA 20-949
From: Robin A. Huff, Ph.D., Supervisory Pharmacologist
Date: February 7, 2001
Re: Accuneb Labeling Revision

This memo revises the dose comparisons made in the preclinical sections of labeling to reflect that the product is indicated for use in a patient population down to 2 years of age. The original calculations were based on an indicated patient population down to 6 years of age.

The following revisions should be made:

Carcinogenesis, Mutagenesis, and Impairment of Fertility:

— ' becomes "...approximately equivalent to..."

— .." becomes "... approximately 140 times..."

— " becomes "...approximately 20 times..."

— " becomes "...approximately 30 times..."

Pregnancy:

Dose comparisons remain the same in this section, except ". — becomes "...approximately 60 times...".

Overdosage:

— ." becomes "...approximately 580 times..."

— ' becomes "...approximately 260 and 1200 times"

cc: NDA 20-949 Division File
/HFD-570 Hilfiker
/HFD-570 Huff

11/10/00

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-949

Dey Laboratories, L.P.
2751 Napa Valley Corporate Drive
Napa, CA 94558

Attention: Peggy J. Berry
Regulatory Affairs Manager

Dear Ms. Berry:

We acknowledge receipt on October 30, 2000, of your October 27, 2000, resubmission to your new drug application (NDA) for AccuNeb (0.63 and 1.25 mg albuterol sulfate) Inhalation Solutions.

This resubmission contains additional information submitted in response to our June 6, 2000, action letter.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is April 30, 2001.

If you have any questions, call Mr. David Hilfiker, Regulatory Project Manager, at (301) 827-1084.

Sincerely yours,

/S/

Sandy Barnes
Chief, Project Management Staff
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

/s/

Sandra Barnes
11/10/00 01:32:17 PM

RECORD OF TELEPHONE CONVERSATION

Date:	August 16, 2000
Project Manager:	Hilfiker
Subject:	**Information Needed to Support Altered Paper Label Plans**
NDA:	20-949 [ ]
Sponsor:	Dey L.P.
Product Name:	AccuNeb [ ]

Approvable (AE) letters were recently issued to the sponsor for both NDAs. The sponsor has not yet filed a complete response. In the last action letters, there were several deficiencies concerning the proposed [ ] Rather than address the deficiencies, Dey has proposed attachment of paper labels to the outside of the overwrap, and the vials.

Dey provided a flow diagram that depicts the proposed drug product manufacturing process with respect to the paper label attachment to the overwrap (see attachment 1). Vibhakar Shah, CMC reviewer, and I contacted Dey to comment on the information that may be necessary to address the proposed drug product design.

FDA Participants:	David Hilfiker	Project Manager
	Vibhakar Shah	CMC Reviewer
Dey Participants:	Peggy Berry	Regulatory Affairs
	Imtiaz Chaudry	Scientific Affairs
	Salisa Poon	Regulatory Affairs

Dey stated that they intend to submit this modified drug product manufacturing process as part of the upcoming response to the FDA action letters. Dey stated that leachables and extractables pertaining to the overwrap and packaging components will be qualified regardless of the outcome of the paper label proposal.

FDA stated that Dey should provide the following to address the proposal to attach the paper label to the outer layer of the foil overwrap pouch:

1. Qualitative composition of all paper label components and applicable references to indirect food additive CFR regulations for paper label components as appropriate. Alternatively, Dey may provide authorized DMF references for this information.

2. Acceptance criteria (with appropriate test methods) for all incoming paper label materials.

FDA asked for assurance that components of the paper label will remain consistent. Dey stated that they are proposing this drug product design because they cannot assure that components of the paper label will not change. Dey believes that the foil overwrap will serve as an absolute barrier [ ] from the paper label into the drug product. FDA

reminded Dey that the DMF for the foil- : overwrap has been found inadequate in support of their applications.

FDA stated that Dey should respond appropriately to the deficiencies in the action letters, retain the proposed acceptance criteria , and support these acceptance criteria with available data.

Dey agreed to provide qualitative composition of paper label components and acceptance criteria that are based on identity testing for incoming materials. Dey also agreed to provide references to indirect food additive regulations as appropriate. Dey stated that a new paper label, different from what has been proposed previously in these NDAs, will be proposed in the resubmission.

David Hilfiker
Project Manager

/S/ 8-25-00

Attachments: (1) August 10, 2000, facsimile correspondence from Dey L.P. (2 pages, hard copy only)

Cc: Original NDAs 20-949
HFD-570/Division files
HFD-570/Hilfiker
HFD-570/Shah/8-24-00
HFD-570/Kim
HFD-570/Poochikian

Initialed by: HFD-570/Schroeder (for Poochikian)/8-25-00
C:\my_documents\N20949\000824tel

RECORD OF TELEPHONE CONVERSATION

Date:	July 18, 2000
Project Manager:	Hilfiker
Subject:	Use of Paper Labels on Drug Product Overwrap
NDAs:	20-949
Sponsor:	Dey L.P.
Product Name:	AccuNeb

Both applications are pending. Approvable letters were issued for NDA 20-949 on June 6, 2000, One of the major unresolved issues has to do with Dey's proposed use of a paper label, adhered to the outer wall of the LDPE vial. Several CMC deficiencies listed in the above approvable letters involve unknown extractable or leachable compounds which may ingress as a result of the paper label components.

Dey has proposed alternatively placing a paper label to the outer side of the overwrap foil pouch and has asked what information needs to be provided as a response to the above action letters in terms of the alternate proposal.

I consulted with CMC reviewers Vibhakar Shah (20-949) and Chong-Ho Kim (20-950), and team leader Guirag Poochikian, and called Peggy Berry, Dey L.P. Regulatory Affairs Director, with the information.

I informed Ms. Berry that the following items are needed for clarification prior to addressing the question:

> Provide the manufacturing operation sequence for the packaging of LDPE vials, including overwrapping, labeling and other associated packaging operations, if any.
>
> Clarify the stage of the manufacturing operation at which the paper labels are affixed (e.g., on the foil- stock, on the unsealed overwrap pouch, on completely sealed pouch, etc.).

POST-TELECONFERENCE NOTE:

I informed Ms. Berry during the teleconference that Dey may submit this information as part of their response to the above action letters. Dr. Shah has informed me that the CMC staff would like these items of clarification prior to the response. Based on the clarification, the CMC staff will determine what further information is necessary to be provided with the response to the action letter. I informed Ms. Berry on July 26, 2000, of this correction. She acknowledged that Dey will provide clarification on the alternative proposal for paper labels on the overwrap and wait for the Division's response to determine what information is needed for their response to the action letter.

David Hilfiker
Project Manager

/S/ 8/2/00

Cc: Original NDAs 20-949
HFD-570/Division file
HFD-570/Hilfiker
HFD-570/Shah/7-25-00/8-1-00
HFD-570/Kim/8-2-00
HFD-570/Poochikian/8-2-00
HFD-570/Meyer

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

RECORD OF TELEPHONE CONVERSATION

Date:	June 12, 2000
Project Manager:	Hilfiker
Subject:	**Clarifications to AE letter**
NDAs:	20-949
Applicant:	Dey Laboratories
Product Name:	AccuNeb

Dey Participants:	Muhammad Asif	Analytical Development
	Partha Banerjee	Inhalation Product Development
	Peggy Berry	Regulatory Affairs
	Imtiaz Chaudry	Scientific Affairs
	Cemal Kemal	Analytical Development
	Cal McGoogan	Quality Control
	Salisa Poon	Regulatory Affairs
	Charles Rice	President and CEO
FDA Participants:	David Hilfiker	Regulatory Project Manager
	Martin Himmel	Deputy Division Director
	Chong-Ho Kim	CMC Reviewer
	Robert Meyer	Division Director
	Guirag Poochikian	CMC Team Leader
	Vibhakar Shah	CMC Reviewer
	Joseph Sun	Pharmacology/Toxicology Team Leader
	Virgil Whitehurst	Pharmacology/Toxicology Reviewer

Dey Laboratories (herein referred to as DEY) was issued approvable (AE) letters for NDAs 20-949, AccuNeb (albuterol sulfate) Inhalation Solution, on June 6, 2000, [redacted]

[redacted] The comments are provided in italics, following by DEY's response (bold) and any discussion which followed.

1. *The following comments pertain to the drug substance, albuterol sulfate.*

   d. *Although [redacted] is regarded as a [redacted] impurity, it is also a potential degradation product. Revise method [redacted] to resolve the [redacted] from albuterol and to achieve accurate quantitation. Alternatively, analyze the drug product at release and through shelf-life (at accelerated and long-term storage conditions) concurrently by both [redacted] and provide the data to ensure that the formation [redacted] does not increase with time and that it remains below the proposed specification, [redacted]. If*

the data prove unequivocally that — is not formed or increased with storage, method ' may be used as is. Alternatively, adopt methods for the quantitation of impurities/degradation products in the albuterol sulfate inhalation solution.

e. *With reference to the chromatogram provided with method ', specify the peak(s) eluting prior to — and the unresolved — — ', Figure 1, p. 0142/Vol. 5). For a chromatographic method, as requested earlier, complement the complete run time chromatogram with an expanded region of the chromatogram that captures where most peaks of interest elute (—*

Method is only used for the AccuNeb product. Did the FDA intend for this question to also apply — specific method or was this question inadvertently included and should be addressed as a part of the AccuNeb response?

Dr. Kim clarified that comment 1.d. applies — method . Comment 1.e. does not apply — , and should only be addressed in the AccuNeb response.

2. *The specification — proposed for — in the drug substance can not be finalized until it is qualified at an appropriate level. (comment 2.b.)*

Dr. Kim emphasized that — is beyond the qualification threshold of 0.1% w/w for drug substance impurities. Dr. Sun added that — is a structural alert for mutagenesis; therefore, genetic toxicology studies, specifically the Ames test and a chromosome aberration assay, will be needed, in addition to the typical 90-day inhalation toxicology study in one appropriate animal species.

DEY asked if qualification of this impurity can be conducted as a Phase 4 commitment, since has an established safety record in its substantial period of consumer use. Dr. Meyer indicated that the Division would consider this request and respond at a later date.

Dr. Whitehurst reminded DEY that literature references may be able to replace some of the studies required for qualification, if there is literature specific to the genotoxicity of this compound.

3. *The following comments pertain to the drug product specifications.*

d. *As previously requested, the — impurities on stability should be limited to — respectively. (comments 3.c. and 7.f.)*

Dey agrees to the requested limit of [ ] impurities on stability. We also plan to comply with 3c and establish an independent specification for [ ] which will not be part of the total impurities. Does the FDA agree with this approach?

Dr. Kim responded that [ ] should be part of the specification for total impurities.

9. *The following comments pertain to the potential leachables of the proposed packaging components [ ] into the drug product.*

   a. *Comparison of the chromatographic data provided for the placebo samples within themselves [ ] Figures 1-18, pp. 0196-0213/Vol. 6) and with the drug product samples (Figures 19-32, pp. 0214-0227) [ ]*

]

Dey agrees with the FDA's comment that several very small peaks were observed in the study previously reported. However, that study was done using [ ] overwrap. Recent work has shown that the vendor's process [ ] overwrap causes the internal overwrap surface to [ ] Therefore, Dey plans to use overwrap [ ] Given this information, we will not rely on the previous study results. A new study was initiated using unlabeled vials and unprinted overwrap. If any small peak(s) is(are) observed, its amount will be estimated as a percent of the drug utilizing ICH Q3A and ICH Q3B guidelines for identification and qualification. Is this approach acceptable to the FDA?

Dr. Shah stated that the Q3A and Q3B guidelines are intended for drug substance-related impurities, not contaminants. DEY must identify and quantify (per container) any contaminants. Once the identity and quantity of a contaminant is known, then FDA can determine whether qualification is necessary.

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

that were used in the clinical studies for these applications. Dey has not. Dr. Poochikian referred DEY to the draft Guidance for Industry entitled "Nasal Spray and Inhalation Solutions, Suspensions, and Spray Drug Products," which asks for this information to be incorporated in the labeling for these products. The proposed package insert should identify the specific nebulizers used in the clinical studies. Dr. Poochikian encouraged DEY to conduct some basic *in vitro* testing of the nebulizer(s) for information that can be incorporated into labeling, as per the draft Guidance.

Also under the section entitled "BACKGROUND INFORMATION" in DEY's June 9 facsimile correspondence, Dey asked for FDA feedback on the following comment.

6. **Pursuant to the Guidance for Industry "Classifying Resubmissions in Response to Action Letters," and in consideration of Dey's above statements characterizing the nature and extent of the response, Dey requests that the FDA consider Dey's complete response to the 2 June letter to be a "Class 1 Resubmission" rather than a major amendment.**

Mr. Hilfiker indicated that the Division usually reserves Class 1 resubmissions for minor changes to the proposed draft labeling only. Therefore, DEY's response will not qualify as a Class 1 resubmission. Mr. Hilfiker committed to confirm this with the Division management after this telephone conference and provide DEY with confirmation of this decision.

POST TELECONFERENCE NOTES

1. DEY requested that FDA allow qualification of ——— as a Phase 4 commitment (see discussion under comment 2). Dr. Meyer indicated that the Division would consider this request and respond at a later date. After discussion with John Jenkins, Office Director, Dr. Meyer believes that we may entertain post-approval qualification IF DEY can prove that their product contains less ——— than their reference product (Atrovent). This is analogous to the situation for qualification of a ——— impurity in DEY's pending AccuNeb ———.

2. DEY asked if they can use 505(b)(2) regulations to reference the finding of safety and effectiveness of a product previously approved by FDA with the same overwrap materials as DEY proposes to use, [redacted] Dr. Meyer stated that the Division would discuss this further internally and respond at a later date. Dr. Meyer discussed this proposal with Dr. Jenkins, and believes that DEY should address extractables and leachables for their drug products in their responses, and that 505(b)(2) references to cover a packaging component of the proposed drug products are not appropriate. Our

previous finding of safety and effectiveness for a drug product in the same overwrap does not allow us to conclude that the interaction of the overwrap with the proposed products, under different manufacturing conditions, are the same.

I communicated these responses to DEY on June 20, 2000. DEY inquired about the possibility that a complete response may be classified as a Class 1 resubmission under the Guidance for Industry (see item 6 under BACKGROUND INFORMATION in the attachment). Mr. Hilfiker confirmed that the Division policy is to reserve Class 1 resubmissions for situations when only labeling modifications are outstanding. In the case of these NDAs, a complete response will require more information and will therefore not be classified as Class 1.

Minutes drafted by: HFD-570/Hilfiker/6-15-00
Initialed by: HFD-570/Sun/6-19-00
HFD-570/Himmel/6-19-00
HFD-570/Meyer/6-19-00

Attachment: 6-9-00 facsimile correspondence from DEY (4 pages, hard copy only)

Cc: Original NDAs 20-949
HFD-570/Division file
HFD-570/Hilfiker
HFD-570/Kim/6-16-00
HFD-570/Shah/6-16-00
HFD-570/Poochikian/6-16-00
HFD-570/Whitehurst/6-19-00
HFD-570/Huff/6-19-00

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Memorandum

To: NDA 20-949
From: Robin A. Huff, Ph.D., Pharmacology Supervisor
Date: June 1, 2000
Re: Labeling Changes (Dose Comparisons)

This is the second review cycle for Accuneb, which is an inhalation solution of albuterol sulfate, a beta-2 agonist, intended for treatment of asthma in children 2 - 12 years of age. The maximum dose is 1.25 mg QID which equates to 0.25 mg/kg/day for a 20 kg child. The final labeling to be sent to the sponsor has been modified from versions found in earlier pharm/tox reviews so that dose comparisons made in the preclinical sections refer only to the pediatric dose, as this product is not intended for adults. In consultation with Drs. Himmel and Meyer it was decided to apply this approach to all preclinical sections of the labeling including the impairment of fertility and pregnancy sections. It was also decided for sake of clarity to deviate slightly from the Division's standard dose comparison language. The language decided on was, "approximately X times the maximum recommended daily inhalation dose of Accuneb on a mg/m^2 basis)."

cc:
HFD-570 Division File
/RHuff
/VWhitehurst
/DHilfiker

NIHIRU-

Memorandum of Telephone Facsimile Correspondence

Date: February 8, 2000

To: Peggy Berry
Regulatory Affairs Manager

Fax No.: 707-224-1364

From: David Hilfiker
Project Manager

Through: Daniel O'Hearn
Medical Officer

Subject: Information Request for Pending NDA 20-949

# of Pages: 2

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

David Hilfiker
Project Manager
Division of Pulmonary Drug Products

cc: ORIG NDA 20-949
HFD-570/Div File
HFD-570/Hilfiker
HFD-570/O'Hearn

c:/my_documents/N20949/00-02-08.irltr.doc

We request the following information for our ongoing review of your December 3, 1999, response to NDA 20-949.

1. Specify the type of compressor that was used with the Pari LC Plus Nebulizer in study DL-019.

2. Clarify the terminology "skin/appendage infection," used to describe certain adverse events observed in study DL-019. Provide the specific diagnosis for each event listed in this category.

Please call to provide me with a timeframe for submitting a response. To expedite our review, it will be helpful if you can fax the response prior to sending it. Thank you for your continued cooperation.

David Hilfiker
Regulatory Project Manager
301-827-1084

APR 27 2000

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: January 14, 2000	**DUE DATE:** May 1, 2000	**OPDRA CONSULT #:** 00-0018

TO: Robert J. Meyer, M.D.
Director, Division of Pulmonary and Allergy Drug Products
HFD-570

THROUGH: David Hilfiker, Project Manager
HFD-570

PRODUCT NAME: AccuNeb (albuterol sulfate inhalation solution; 0.63 mg, 1.25mg per 3 mL) **NDA #:** 20-949	**MANUFACTURER:** DEY, L.P. Napa, CA 94558

SAFETY EVALUATOR: Carol Pamer, R.Ph.

SUMMARY: In response to a consult from the Division of Pulmonary and Allergy Drug Products (HFD-570), OPDRA conducted a review of the proposed proprietary name "AccuNeb" to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION: From a safety perspective, OPDRA has no objections to the use of the name "AccuNeb", but with some reservation (see attached review). The established name of this and related albuterol inhalation solution products be revised to conform to the USP/NF nomenclature standards. We have also made recommendations for labeling revisions to minimize potential errors with the use of this product. See the checked box below.

☐ FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW
This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDAs from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

☒ FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW
OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDAs from this date forward.

☐ FOR PRIORITY 6 MONTH REVIEWS
OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDAs from this date forward.

/S/ 4/27/2000
Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

/S/ 4/28/00
Peter Honig, M.D.
Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Postmarketing Drug Risk Assessment (OPDRA)

HFD-400; Parklawn Building Room 15B-03

FDA Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: April 12, 2000

NDA NUMBER: 20-949

NAME OF DRUG: AccuNeb (albuterol sulfate inhalation solution; 0.63 mg [base]/3 mL, 1.25 mg [base]/3 mL)

NDA HOLDER: DEY, L.P.
Napa, CA 94558

I. INTRODUCTION

This consult was written in response to a request from the Division of Pulmonary and Allergy Drug Products (HFD-570) for assessment of the tradename AccuNeb. The sponsor initially submitted the proprietary name AccuNeb for review by the FDA Labeling and Nomenclature Committee (LNC). The LNC found this name to be "Acceptable" on November 23, 1998.

AccuNeb is an albuterol sulfate solution for inhalation. This product is supplied in two strengths: 1.25 mg albuterol base per 3 mL (0.042%) and 0.63 mg albuterol base per 3 mL (0.021%). AccuNeb is indicated for the relief of bronchospasm in patients with asthma (reversible obstructive airway disease) . Clinical trials were conducted with AccuNeb in patients between 6 and 12 years of age. The recommended maintenance dosage for patients is 1.25 mg or 0.63 mg albuterol base, administered 3 or 4 times daily by nebulization.

In the U.S., two additional strengths of albuterol sulfate inhalation products are available. Proventil™ was approved on January 14, 1987 (Schering) as a 0.5% (base) inhalation solution and 2.5 mg albuterol base per 3 mL (0.083%) inhalation solution. Ventolin™ (Glaxo Wellcome) is available in the same concentrations. Generic equivalents of these products are marketed in the U.S. also. The indications for these products are the same as listed for AccuNeb. These products, however, are approved only for use in adults and children 12 years of age and older. The usual dosage is 2.5 mg albuterol base, administered 3 or 4 times daily by nebulization. In the case of the 0.5% inhalation solution, 0.5 mL (2.5 mg albuterol base) of the product should be diluted to a total volume of 3 mL with sterile normal saline. The 0.083% inhalation solution contains 2.5 mg per 3 mL and, therefore, does not require dilution.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[i,ii,iii] as well as several FDA databases[iv] for existing drug names which sound alike or look alike to AccuNeb to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[v]. An Expert Panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three (3) prescription analysis studies, to simulate the prescription ordering process.

A. EXPERT PANEL DISCUSSION

A group discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name AccuNeb. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

One proprietary name for an over-the-counter nutritional supplement product, Accupep HPF (Sherwood Medical), was identified that was thought to bear some resemblance to AccuNeb. However, a consensus was reached that the sound-alike, look-alike properties were minimal. Confusion of this product with AccuNeb seems unlikely also, due to the differences in dosage forms, route of administration, and different markets (OTC vs. Rx only).

[redacted] *The potential for medication errors is increased with the similarity in naming as compared with AccuNeb. This naming pattern is particularly concerning if requests for additional related drug names are received.*

B. STUDY CONDUCTED BY OPDRA

1. Methodology

A study was conducted within FDA employing a total of 92 health care professionals (nurses, pharmacists, physicians) to determine the degree of confusion of AccuNeb with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. This exercise was conducted in an attempt to simulate the

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[i] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Co. Inc, 2000).

[ii] American Drug index, 42nd Edition, 1999, Facts and Comparisons, St. Louis, MO.

[iii] Facts and Comparisons, 2000, Facts and Comparisons, St. Louis, MO.

[iv] COMIS, The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and online version of the FDA Orange Book.

[v] WWW location http://www.uspto.gov/tmdb/index.html.

[vi] **Note: Any and all information pertaining to [redacted] is protected under privacy laws and, therefore, is not releasable at this time. Redacting prior to FOI releases will be necessary.**

prescription ordering process. An OPDRA staff member wrote outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and prescriptions for (see below). These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one OPDRA staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTIONS
Outpatient: AccuNeb 3 mL po t.i.d., 2 refills	*Outpatient*: Accuneb 3 mLs p.o. three times daily, 2 refills
Inpatient: Accuneb 3 mL t.i.d.	

2. Results

Results of this exercise are summarized below:

Study	No. of participants	# of responses (%)	"Accuneb" response	Other response
Written: Outpatient	31	21 (68%)	20 (95%)	1 (5%)
Inpatient	30	14 (47%)	12 (86%)	2 (14%)
Verbal: Outpatient	31	16 (52%)	4 (25%)	12 (75%)
Total	92	51 (55%)	36 (71%)	15 (29%)

Among participants in the two (2) written prescription studies, the majority of the respondents (32 of 35; 91%) interpreted the name correctly. The other name interpretations generally were phonetic variations of AccuNeb.

Among verbal prescription study participants, 4 respondents (13%) interpreted the name correctly. Most of the incorrect name interpretations were phonetic variations of "Accuneb", including 6 respondents (19%) who interpreted the name as "Acuneb".

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "AccuNeb", the primary concern raised was related to the use of the phrase "Neb" for multiple products, e.g. AccuNeb —— (OPDRA consult #00-0020, —). *Although the consensus was reached that AccuNeb — were significantly distinct product names, the potential for medication errors is increased with the similarity in naming. This would be particularly concerning if requests for additional related drug names are received.*

We conducted prescription studies in an attempt to simulate the prescription ordering process. In this exercise, there were no erroneous interpretations of this proprietary name with other U.S. marketed drug products.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the container labels, carton labeling, and draft package insert for AccuNeb, OPDRA has attempted to focus on safety issues relating to possible medication errors. We have identified areas of possible improvement, in the interest of minimizing potential user error.

A. DRUG NOMENCLATURE ISSUES

1. **We have concerns regarding the established name of this product**, particularly in consideration of the two existing forms of albuterol sulfate inhalation solution. One of these relates to the designation of strength and dosing of the products as albuterol base. Conversion to the sulfate content is included in the labeling as well (see Description). The established name is designated as "albuterol sulfate inhalation solution". **With the pending approval of AccuNeb and its two additional concentrations of albuterol (sulfate) inhalation solution, both the opportunity and need exist to revise the established name to conform to the current USP/NF standards. We recommend, therefore, that the established name of all of these products be changed to "albuterol inhalation solution".**

2. The strength of the previously approved products is expressed as a w/v% of albuterol base, with a mg/mL content provided as well. The new AccuNeb products do not include the percentage strength in the labeling. The approval of AccuNeb will add 2 additional product strengths to the existing forms of albuterol (sulfate) inhalation solution. *With multiple concentrations of this product being available, differences in how both strength and dosing are expressed, and similar-appearing unit-dose 3 mL vials for nebulization, medication errors involving these products seems likely.* This could result in both underdosing of adults, as well as overdosing of pediatric patients.

   We understand that the Division (HFD-570) has previously requested that the sponsor convert this designation of strength to the mg-content only. We agree with this request, since dosing would frequently be expressed as milligrams of albuterol base. Optimally, the previously approved products should also be revised to conform to this format. In the interim, however, **we suggest that the strength as percentage also be expressed, to help minimize confusion with the existing, more concentrated products. We suggest the following format:**

   For AccuNeb: Albuterol inhalation solution, 1.25 mg/3mL (0.042%)
   Albuterol inhalation solution, 0.63 mg/3mL (0.021%)

   For Proventil,: Albuterol inhalation solution, 2.5 mg/3mL (0.083%)
   Ventolin, Albuterol inhalation solution, 0.5%
   generics

   Inclusion of this total mg-content per volume would result in accurate communication of prescriptions. For example, under the current nomenclature, a pharmacist would now require clarification on a prescription written for "albuterol 1.25 mg 4 times daily via nebulizer". Formerly, only one pre-mixed nebulized dosage form was available or the prescriber would often indicate that albuterol 0.5% solution was to be diluted with normal saline to 3 mL. With the approval of AccuNeb, this dose could be interpreted as an AccuNeb 1.25 mg/3 mL vial, two AccuNeb 0.63 mg/3 mL vials, or Proventil (et. al.) half of a 2.5 mg/3mL vial. *The volume of fluid intake and the rate of drug delivery would be affected.*

   Including percentage strength would provide additional clarification and flexibility for the prescriber, as prescriptions could also be expressed as milliliters of particular product. An example would be "AccuNeb/albuterol inhalation solution 0.041%, 3 mL 4 times daily via nebulizer" or "Proventil/albuterol inhalation solution 0.083%, 3 mL 4 times daily via nebulizer".

B. CONTAINER LABELING (0.63 mg & 1.25 mg vials)

1. See changes as recommended above.

C. CARTON LABELING AND PACKAGE INSERT LABELING (0.63 mg & 1.25 mg vials; 5-,25-, 30-unit cartons)

1. Under DESCRIPTION in the package insert, we recommend the following revised statements, for consistency with the USP/NF guidelines:

   a. For AccuNeb ™ 1.25 mg:

   "Each mL of AccuNeb™ (1.25 mg) contains *albuterol sulfate equivalent to 0.42 mg albuterol* in an isotonic...between 3 and 5".

   b. For AccuNeb ™ 0.63 mg:

   "Each mL of AccuNeb™ (0.63 mg) contains *albuterol sulfate equivalent to 0.21 mg albuterol* in an isotonic...between 3 and 5".

   Please note also that, as currently stated, a base-to-sulfate conversion error is present: "0.21 mg of albuterol base (as **0.5 mg** of albuterol sulfate)" should appear as **0.25 mg** of albuterol sulfate.

2. As the Indications for AccuNeb are currently stated, it is not clear that AccuNeb products are intended for use only in pediatric patients (e.g., 2 to 12 y.o., personal communication HFD-570).

3. See changes as recommended above.

APPEARS THIS WAY
ON ORIGINAL

IV. RECOMMENDATIONS

A. From a safety perspective, OPDRA does not object to the use of the proprietary name "AccuNeb", but with a noted reservation.

B. We have made recommendations for labeling revisions to minimize potential errors with the use of this product.

C. We recommend that, at this time, the established name of this and related albuterol inhalation solution products be revised to conform to the USP/NF nomenclature standards.

OPDRA would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Carol Pamer, R.Ph. at 301-827-3245.

/S/

Carol Pamer, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

/S/ 4/27/2000

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

cc: NDA 20-949
HFD-570; Division Files/Hilfiker, Project Manager
HFD-570; Robert Meyer, Division Director
HFD-040; Mark Askine, Senior Regulatory Review Officer, DDMAC
HFD-430; Claudia Karwoski, Team Leader, OPDRA
HFD-400; Carol Pamer, Safety Evaluator, OPDRA
HFD-400; Peter Honig, Director, OPDRA (electronic copy)
HFD-400; Jerry Phillips, Associate Director, OPDRA
HFD-002; Murray Lumpkin, Deputy Center Director for Review Management (electronic copy)

L:\OPDRA00\PAMER\000018ACCUNEB.fin.DOC

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

REQUEST FOR CONSULTATION

Assn # 800 Line 1153

TO (*Division/Office*): HFD-160/ONDC/Cooney			FROM: HFD-570/DPADP/Hilfiker	
DATE: January 20, 2000	IND NO.:	NDA NO.: 20-949	TYPE OF DOCUMENT: Major Amendment	DATE OF DOCUMENT: December 3, 1999
NAME OF DRUG: AccuNeb (albuterol) Inhalation Solution	PRIORITY CONSIDERATION: standard	CLASSIFICATION OF DRUG: 5S	DESIRED COMPLETION DATE: May 1, 2000	

NAME OF FIRM: Dey Laboratories

REASON FOR REQUEST

I. GENERAL

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

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 REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER:

P/S DK 1/24/00

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JAN 21 2000
HFD-160

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILITY 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: Refer to Hussong's comments (18.a-f.) in the March 30, 1999, AE letter (given in the submission). Please review the company's responses to these comments.

cc: Original NDA 20-949
HFD-570/Div. Files
HFD-570/Hilfiker, Shah

SIGNATURE OF REQUESTER: DA 1/20/99	METHOD OF DELIVERY (Check one): ■ MAIL ☒ HAND
SIGNATURE OF RECEIVER:	SIGNATURE OF DELIVERER: 1/21/00

1-21-00

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

REQUEST FOR CONSULTATION

ivision/Office): **HFD-400/OPDRA/Associate Director for ...edication Error Prevention**			FROM: **HFD-570/DPADP/Hilfiker**	
DATE: January 11, 2000	IDA NO.:	NDA NO.: 20-949	TYPE OF DOCUMENT: Complete Response to AE letter	DATE OF DOCUMENT: December 3, 1999
NAME OF DRUG: AccuNeb	PRIORITY CONSIDERATION: standard		CLASSIFICATION OF DRUG: 3S	DESIRED COMPLETION DATE: May 1, 2000

NAME OF FIRM: Dey Laboratories

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ ...NTROLLED STUDIES ☐ ...OTOCOL REVIEW ☐ ...HER:	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER:

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY 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: LNC has previously found this tradename to be acceptable (consult 1092b, signed by D. Boring on 11-23-98).

cc: Original NDA 20-949
HFD-570/Div. Files
HFD-570/Hilfiker, Shah, O'Hearn, Whitehurst

SIGNATURE OF REQUESTER: (...)	METHOD OF DELIVERY (Check one): ■ MAIL ☐ HAND
SIGNATURE OF RECEIVER:	SIGNATURE OF DELIVERER:

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT #	1092b	HFD#	570	PROPOSED PROPRIETARY NAME:	PROPOSED ESTABLISHED NAME:
ATTENTION:	David R. Hilfiker			Accuneb	albuterol sulfate/

A. Look-alike/Sound-alike

Potential for confusion:

____ Low ____ Medium ____ High

____ Low ____ Medium ____ High

____ Low ____ Medium ____ High

____ Low ____ Medium ____ High

____ Low ____ Medium ____ High

B. Misleading Aspects:

C. Other Concerns:

D. Established Name

xxx Satisfactory

____ Unsatisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations:

XXX ACCEPTABLE ____ UNACCEPTABLE

F. Signature of Chair/Date S 4/23/98

JAN - 4 2000

NDA 20-949

Dey Laboratories, L.P.
2751 Napa Valley Corporate Drive
Napa, CA 94558

Attention: Peggy J. Berry
Regulatory Affairs Manager

Dear Ms. Berry:

We acknowledge receipt on December 6, 1999, of your December 3, 1999, resubmission to your new drug application (NDA) for Accuneb (albuterol sulfate) Inhalation Solution, 0.021% and 0.042%.

This resubmission contains additional information submitted in response to our March 30, 1999, action letter.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is June 6, 1999.

If you have any questions, contact Mr. David Hilfiker, Project Manager, at (301) 827-1084.

Sincerely yours,

/S/

Parinda Jani
Acting Chief, Project Management Staff
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 20-949
HFD-570/Div. Files
HFD-570/Hilfiker
HFD-570/O'Hearn
HFD-570/Himmel
HFD-570/Shah
HFD-570/Poochikian
HFD-570/Whitehurst
HFD-570/Huff
HFD-570/Wilson
HFD-570/Chen
HFD-570/Uppoor
DISTRICT OFFICE

/S/ 1-4-00

/S/ 1/4/00

Drafted by: HFD-570/Hilfiker/December 14, 1999
Initialed by: HFD-570/Jani
Final: HFD-570/Hilfiker/1-4-00
Filename: c:\my_documents\N20949\99-12-14.acltr.doc

CLASS 2 RESUBMISSION ACKNOWLEDGEMENT (AC)
(DDR: Update the user fee goal date based on the class of resubmission.)

MAR 2 2 1999

MEMO TO THE FILE

NDA # 20-949
Drug: —— (albuterol sulfate) Inhalation Solution, 0.75 mg and 1.50 mg
Applicant: Dey Laboratories

Letter Date: March 27, 1998
Receipt Date: March 30, 1998
Due Date: March 31, 1999

Subject: LABELING COMMENTS

This application is approvable (AE) with major deficiency comments to be sent to the applicant. Most of the review disciplines decided to withhold specific labeling comments until the applicant's response to this AE letter is reviewed. No specific labeling comments and no marked-up draft labeling are going to be sent to the applicant in this cycle.

However, several reviews did include specific labeling comments. These comments will be deferred until the next cycle. Refer to the list below for the reviews that need to be referenced for specific labeling comments in the next cycle.

Clinical Pharmacology & Biopharmaceutics Review
Reviewer: Albert Chen/HFD-870
Stamp Date: March 18, 1999

Pharmacology & Toxicology Review
Reviewer: Virgil Whitehurst/HFD-570
Stamp Date: December 21, 1998

David Hilfiker
Project Manager

/S/ 3-22-99

Cc: Original NDA 20-949
HFD-570/Division File
HFD-570/Hilfiker
HFD-570/Schumaker/3-22-99

C:\my_documents\N20949\99-03-22.mem.doc

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: March 19, 1999

FROM: Daniel O'Hearn, M.D.
Division of Pulmonary Drug Products
HFD-570

SUBJECT: NDA 20-949 Accuneb

TO: NDA 20-949 Accuneb File

THROUGH: Martin Himmel, M.D.
Deputy Director, HFD-570

After a review of the NDA for Accuneb and Dr. Himmel's memo, John Jenkins, M.D., Division Director, HFD-570, had the following comments to add to the action letter to the sponsor, Dey Laboratories, L.P.

1. In the four week trial DL-019, it was rather remarkable that after the first dose of drug at Visit 2, the 0.75 mg dose often had higher values than the 1.5 mg dose. This was true regardless of endpoint selected, and in most of the subgroups. Is it possible that the 1.5 and 0.75 mg doses may have been mislabeled at Visit 2 and correctly labeled at Visit 4? It is requested that the sponsor verify that the data in DL-019 1.5 mg and 0.75 mg doses were correctly labeled in DL-019 at Visit 2.

2. With regard to the name of the product, the Division of Pulmonary Drug Products recommends that the sponsor should include the dose, 0.75 and 1.5 mg in the name of the product rather than the concentration. The concentration is very confusing and the Division of Pulmonary Drug Products has been working to move all the labeling for inhalation products to be based on the dose.

3. The Division of Pulmonary Drug Products does not want to receive Nonlinear Mixed Effects Models (NONMEM) analyses of clinical trial data in the future as pivotal analyses. The Division of Pulmonary Drug Products expects more conventional analyses (e.g., ANOVA) in such pivotal analyses.

N-20449/HiFiker

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Michael Noonan, M.D.
545 NE 47th, Suite 310
Portland, Oregon 97213

MAR 16 1999

Dear Dr. Noonan:

On November 9-19, 1998, Ms. V. Teres Speer, representing the Food and Drug Administration (FDA), conducted an inspection of your conduct, as investigator of record, of a clinical study (Protocol No. DL-019) of the investigational drug —— (albuterol sulfate) Inhalation Solution 0.042% and 0.021% performed for Dey Laboratories. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of these studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we find some deviations from federal regulations and/or good clinical investigational practices. These deviations were listed for you on the Form FDA 483 and discussed with you at the close of the inspection. The deviation included the failure to follow the protocol in that post-dose tests and days between subjects' visits were outside of the protocol specified time periods. We acknowledge the explanations you provided during the exit interview; your explanations will be included as part of the inspection records. We expect, as you stated, that corrective measures will be instituted to assure that the deviations listed on the Form FDA 483 are not repeated in any of your ongoing or future studies.

We appreciate the cooperation shown Ms. Speer during the inspection.

Sincerely yours,

(S)

Bette L. Barton, Ph.D., M.D.
Chief
Clinical Investigations Branch
Division of Scientific
Investigations
Office of Compliance
Center for Drug Evaluation
and Research

cc:
HFA-224
HFD-570 Doc. Rm. NDA 20-949
HFD-570 Review Div. Dir.
HFD-570 MO (O'HEARN)
HFD-570 PM (HILFIKER)
HFD-340/R/F
HFD-344/Chron File
HFD-344/CIB File #7036
HFD-344/CIB REVIEWER (JU)
HFD-344/CIB PM (CURRIER)
HFR-PA350 DIB (CORCORAN)
HFR-PA3540 BIMO MONITOR (MATTSON)
HFR-PA350 FIELD INVESTIGATOR (SPEER)

CFN: 3001574
Field Classification: VAI
Headquarters Classification:
_____1)NAI
__X__ 2)VAI-no response required
_____3)VAI-response requested
_____4)OAI

If the Field and Headquarters classifications are different, explain why:

Deficiencies noted:
_____ inadequate consent form
_____ inadequate drug accountability
__X__ deviations from protocol
_____ inadequate records
_____ failure to report ADRs
_____ other (specify)

r/d: HWJ: 01/04/99
reviewed:2/11/99
Finaled: SLK:3/1/99

Note to MO:

1) The calibration of the Koko Spirometer was not performed according to the instruction Manual. Moreover, the instruction video does not match the instruction manual.
2) There is no place on the diary to record concurrent medications and adverse events. All this information was obtained from the parent verbally by the study coordinator and recorded on the CRFs.
3) Discrepancies were observed for drug accountability as

reported in the clinic comments (original data), monitoring reports and sponsor report (data report to FDA) for the following subjects: (exhibit 36 page 7)

#1, 3, 5, 9, 11, 12, 14, 17, 18, 20, 21, 22 and 24

4) Discrepancies were observed for the "number of days between visits" as reported in the CRFs (original data), monitor report and data summary (submitted to FDA) for the following subjects (see exhibit 36, page 3):

#13, 14, 15, 16, 18, 20, 21, 22, 23 and 26

5) Discrepancies were observed for the ±5 minutes tests between the clinical data and the monitor/sponsor reports for the following subjects (exhibits 36, pages 4, 5 and 6):

1, 2, 3, 6, 7, 8, 9, 11, 12, 13, 15, 17, 18, 19, 20, 23, 24, 26, 27 and 28

(Please also see the attached NDA data listing and CIB reviewer's calculations)

6) CIB reviewer's note: The data generated from this study are far from perfect; however, the data appear acceptable to support drug claims.

MEMORANDUM

DATE: March 28, 1999

FROM: John K. Jenkins, M.D.
Director, Division of Pulmonary Drug Products

TO: NDA 20-949

SUBJECT: Overview of NDA Review Issues

Administrative:

NDA 20-949 for albuterol sulfate inhalation solution, 0.042% and 0.21% was submitted by Dey Laboratories on March 30, 1998, as a 505(b)2 application with reference to previously approved albuterol sulfate inhalation solutions. The Division reviewed the NDA as a standard application. The user fee goal date for this application is March 30, 1999.

Clinical:

The primary intent of this application is to gain approval to market unit-dose LDPE vials containing 0.75 mg and 1.5 mg of albuterol sulfate inhalation solution for use in children with bronchospasm. The only currently available unit-dose vials of albuterol sulfate inhalation solution contain 3 mg, therefore, patients who require a lower dose (e.g., due to age, weight, intolerance of higher doses, etc.) must use the multi-dose albuterol sulfate inhalation solution. Potential problems related to use of the multi-dose inhalation solution include microbial contamination and the presence of preservatives to which some patients may cause bronchospasm. In support of the proposed indication (i.e., for

the sponsor submitted the results of three clinical trials conducted in pediatric patients with asthma 6-12 years of age. For a complete review of the details of these trials, please refer to the Medical Officer Review prepared by Dr. O'Hearn and the Medical Team Leader Memorandum prepared by Dr. Himmel.

I concur with Drs. O'Hearn and Himmel that the results of the clinical trials adequately support the safety and effectiveness of albuterol sulfate inhalation solution at doses of 0.75 and 1.5 mg in children 6-12 years of age. I also concur with their assessment that the available data can be extrapolated to children 2-5 years of age such that the indicated age range for the two doses will be 2-12 years of age. The sponsor has not submitted any data to support use of these lower doses in adults and I concur with Dr. Himmel that the

this product in adults.

This application is approvable from a clinical standpoint assuming that the sponsor adequately addresses several minor discrepancies and requests for information as detailed in the Medical Officer's review. These comments will be included in the action letter.

Pharmacology/Toxicology:

The sponsor did not submit any new pharmacology/toxicology data in support of this NDA since albuterol sulfate inhalation solution at higher doses has been approved for marketing for many years and is ANDA eligible. There are outstanding issues related to qualification of certain impurities/degradants and — impurities that may require the conduct of 90-day inhalation toxicology studies and or genotoxicity studies prior to approval of this NDA.

The application is approvable from a pharmacology/toxicology standpoint assuming that the sponsor adequately addresses outstanding issues related to qualification of the safety of several impurities/degradants and — impurities. These comments will be included in the action letter along with recommendations for 90-day inhalation toxicology studies and/or genotoxicity studies.

Clinical Pharmacology and Biopharmaceutics:

The sponsor did not submit any pharmacokinetic data for the proposed doses in children due to the very low levels of albuterol present in systemic circulation following inhalation administration. There are no outstanding issues from a clinical pharmacology and biopharmaceutics perspective.

The application is approvable from a clinical pharmacology and biopharmaceutics standpoint with appropriate labeling.

Chemistry, Manufacturing, and Controls:

As noted above, the sponsor proposes to market albuterol sulfate inhalation solution in LDPE unit-dose vials at doses of 0.75 mg (0.021%) and 1.5 mg (0.042%) per vial. Please see the CMC review prepared by Dr. Shah for complete details regarding this submission. There are numerous CMC deficiencies that must be adequately addressed by the sponsor prior to approval of this application. One significant area of concern is the issue of foreign — into the drug product, a problem that is common to all solution drug products for inhalation package in LDPE vials. The sponsor has identified through its stability testing that — presumably derived from the — used to — overwrap, is found in the drug solution. To address this problem, the sponsor has proposed to employ a new overwrap material that will not contain — into the drug product, however, to date the sponsor had not submitted any data for the new overwrap. Another significant concern for this application is the sponsor's proposal to
This raises serious concerns regarding the potential for — foreign — from the paper labels, the ink, — etc., into

the drug product. These concerns must be adequately addressed by the sponsor prior to approval or the sponsor will need to abandon paper labeling and adopt — of the LDPE vial as is the case for other inhalation solutions approved by the Division.

The application is not approvable from a CMC standpoint. Numerous CMC deficiencies will be included in the action letter.

Data Integrity:

The Division of Scientific Investigations audited three clinical sites that participated in the pivotal 4-week clinical trial in support of this application. One site was rated as NAI and two sites were rated as VAI. Please see the Medical Officer Review for a summary of the discrepancies noted at the two sites that were rated VAI. There were no serious deficiencies noted that would raise a concern regarding the integrity of the clinical database that supports approval.

Labeling:

The sponsor originally proposed that the tradename for this product be — This name was reviewed by the LNC and found to be unacceptable due to its similarity to other currently approved products. The sponsor subsequently proposed Accuneb as the tradename. This name was found to be acceptable by the Division and the LNC, however, the sponsor has not indicated that they plan to move forward with this name. Most recently the sponsor proposed another tradename which has not been reviewed by the LNC. The sponsor will be reminded that they will need to submit their proposed tradename for review prior to approval. General labeling comments will be provided to the sponsor in the action letter. More detailed comments will be provided once the sponsor's response to the deficiencies noted in the action letter have been reviewed. The sponsor will be informed that the product name should include the dose of albuterol sulfate in mg (e.g., 0.75 and 1.5 mg) rather than the concentration of the solution (e.g., 0.021% and 0.042%).

Recommendation:

Overall this application is approvable, however, there are numerous CMC deficiencies and some minor clinical issues that must be addressed prior to approval. The sponsor should receive an APPROVABLE letter listing the outstanding deficiencies.

cc:

NDA 20-949
HFD-570/Division File
HFD-570/Jenkins
HFD-570/Hilfiker
HFD-570/Himmel

INTEROFFICE MEMORANDUM

TO: NDA 20-949

FROM: MARTIN H. HIMMEL, MD, MPH

DEPUTY DIRECTOR, DIVISION OF PULMONARY DRUG PRODUCTS, HFD-570

SUBJECT: SECONDARY REVIEW MEMO FOR NDA 20-949

DATE: MARCH 15, 1999

CC: HFD-570: JENKINS, HIMMEL, OHEARN, HILFIKER, WILSON, ARAS

/S/ 3/16/99

/S/ 3/18/99

Introduction

Dey Laboratories submitted this NDA on March 30, 1998 to obtain approval for a .042% and .021% albuterol sulfate inhalation solution packaged in 3ml unit dose containers. Each ml of the .042% solution contains .5mg of albuterol sulfate and each ml of the .021% solution contains .25mg of albuterol sulfate. Thus, the proposed dosage of this drug would be 1.5 or .75mg of albuterol sulfate, delivered via nebulizer, three or four times daily. The proposed indication is "for the relief of bronchospasm in patients with asthma (reversible obstructive airways disease)

By way of background, there is currently a Ventolin Nebules Inhalation Solution that has been approved by FDA, which has the following indication and dosing instructions:

> INDICATIONS AND USAGE: VENTOLIN NEBULES Inhalation Solution is indicated for the relief of bronchospasm in patients 2 years of age and older with reversible obstructive airway disease and acute attacks of bronchospasm.
>
> DOSAGE AND ADMINISTRATION: Adults and Children 2 to 12 Years of Age: The usual dosage for adults and for children weighing at least 15 kg is 2.5 mg of albuterol (one NEBULE®) administered three to four times daily by nebulization. Children weighing less than 15 kg who require less than 2.5 mg/dose (i.e., less than a full NEBULE) should use VENTOLIN Inhalation Solution instead of VENTOLIN NEBULES Inhalation Solution. More frequent administration or higher doses are not recommended. To administer 2.5 mg of albuterol, administer the entire contents of one sterile unit dose NEBULE (3 mL of 0.083% inhalation solution) by nebulization. The flow rate is regulated to suit the particular nebulizer so that VENTOLIN NEBULES Inhalation Solution will be delivered over approximately 5 to 15 minutes.

The Ventolin Inhalation Solution labeling referred to above recommends a 1.5mg dose in patients weighing less than 15kg. Thus, the FDA has already made a finding that the 1.5mg dose is safe and effective in patients age 2-5 years. This point will be discussed further below regarding the labeling for this drug product.

Safety and Efficacy Data

In support of the safety and efficacy of this drug, the sponsor has conducted three clinical trials. The three studies are a methacholine challenge study, a single dose safety and efficacy

crossover study, and a four-week randomized, placebo controlled trial. The methacholine challenge trial was complicated by two factors:

1. All subjects had to have a baseline PC_{20} of < 4 mg/ml in order to be randomized, yet several subjects had a pre-treatment PC_{20} of > 4 mg/ml, and

2. Several subjects demonstrated a ceiling effect with a post-treatment PC_{20} of > 128 mg/ml (the highest dose administered). The sponsor, therefore, used a nonlinear mixed effects model to analyze the data and the PC_{20} was extrapolated beyond 128 mg/ml.

Because of these problems and the challenge nature of the study, this study provides little data concerning the safety and efficacy of Accuneb. The second study included in this NDA is a single dose, randomized, placebo controlled, crossover study of .75, 1.5 and 3mg of albuterol sulfate in 24 patients age 6-12 years. In summary, all three doses were statistically significantly better than placebo on the primary endpoint of the AUC of the FEV1 change from baseline. In addition, all doses were better than placebo on the AUC of the FEV1 percent change from baseline and the maximum FEV1 percent change. In the medical officer review duration of effect was defined as the amount of time which the FEV_1 was increased by 15% over pre-dose values for at least two contiguous measurements. Using this definition, the .75 and 3mg doses had a 4-hour duration of effect while the 1.5mg dose had a 6-hour duration of effect. No significant side effects that would preclude approval of this drug were noted. Therefore, this study supports the safety and efficacy of Accuneb, at doses of .75 and 1.5mg, in patients age 6-12 years.

The third trial in this NDA is a randomized, double-blind, placebo controlled, parallel group study of .75 and 1.5mg of albuterol sulfate administered three times daily over four weeks to patients age 6-12 years. Of note, when the study was completed there was a good distribution of patients across age groups with approximately 30-35 patients per treatment arm in the 6-8 year group, 40-45 in the 9-10 year group and 30-35 in the 11-12 year age group. Overall, this study demonstrated statistically significant improvement for both doses vs. placebo at the first and last treatment visits on endpoints including percent change in AUC FEV1 and maximum FEV1. The duration of response seen in this study was shorter than that described for the single dose study. After the first dose of drug the duration of effect was between two and three hours for both doses, on a mean basis, although there were responders out to six hours post dose. In addition, while efficacy was seen over the entire course of the trial, on some subset analyses, statistical significance of the .75mg dose vs. placebo was not achieved at the last visit, although the drug was numerically superior to placebo. Overall, this study supports the safety and efficacy of the .75 and 1.5 mg doses of albuterol sulfate in patients age 6-12 years.

In conclusion, the sponsor has submitted in this NDA two clinical trials which support the safety and efficacy of albuterol sulfate, at doses of .75 and 1.5mg given three times daily, in patients age 6-12 years with asthma. The medical officer review includes a number of comments to the sponsor requesting clarification of tables and individual patient data that should be conveyed to the sponsor in the action letter.

Use in Children Age 2-5 years

While the sponsor has not specifically addressed this patient population with clinical trial data, as discussed above, the Agency has already made a finding of efficacy and safety for a 1.5mg dose in patients age 2-5 years for albuterol sulfate. As such, based on this being a 505 (b) (2) application, this finding should apply for the 1.5 mg dose of Accuneb as well. In addition, since the .75mg dose has been shown to be effective in patients age 6-12 in the sponsor's own studies, there is no basis to assume that such a dose would not work in the younger population of 2-5 year olds, particularly since albuterol sulfate has already been shown to work in this age group. As such, this drug can be approved for use in patients age 2-5 as well.

Division of Scientific Investigations (DSI) Audits

As discussed in the medical officer review, three trial sites were audited and there were no findings that call into question the reliability of the data being used to support the approvability of this NDA.

Name

There are no clinical objections to the name Accuneb. In addition, the Labeling and Nomenclature Committee found the name acceptable.

Labeling

A full review of the package insert was not conducted at this time. However, some general comments regarding changes to the package insert have been drafted by the medical officer and should be conveyed as preliminary comments to the sponsor in the action letter.

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Anjuli Seth Nayak, M.D.
Asthma & Allergy Research Associates, S.C.
1300 Franklin Avenue, Suite 180
Normal, Illinois 61761

FEB 19 1999

Dear Dr. Nayak:

On November 17-19, 1998, Ms. Susan D. Yuscius, representing the Food and Drug Administration (FDA), conducted an inspection of your conduct, as investigator of record, of a clinical study (Protocol No. DL-019) of the investigational drug ——— (albuterol sulfate) Inhalation Solution 0.042% and 0.021% performed for Dey Laboratories, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of these studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we concluded that you adhered to pertinent federal regulations and/or good clinical practices governing your conduct of clinical investigations and the protection of human

We appreciate the cooperation shown Ms. Yuscius during the inspection.

Sincerely yours,

/s/

Bette L. Barton, Ph.D., M.D.
Chief
Clinical Investigations Branch
Division of Scientific
Investigations
Office of Compliance
Center for Drug Evaluation
and Research

cc:
HFA-224
HFD-570 Doc. Rm. NDA 20-949
HFD-570 Review Div. Dir.
HFD-570 MO (O'HEARN)
HFD-570 PM (Hilfiker)
HFD-340/R/F
HFD-344/Chron File
HFD-344/CIB File #9692
HFD-344/CIB REVIEWER (JU)
HFD-344/CIB PM (CURRIER)
HFR-CE650 DIB (BAUMGARTEN)
HFR-CE6520 BIMO MONITOR (YUSCIUS)
HFR-CE6520 FIELD INVESTIGATOR (YUSCIUS)

CFN: 1424264
Field Classification: NAI
Headquarters classifications: NAI

r/d: HWJ: 2/4/99
reviewed: BLB:2/4/99
Finaled: SLK:2/17/99

Note to MO: The FEV_1 and FVC data from the NDA were compared with the source records for all 20 study subjects. No discrepancies were noted. Data from this study appear acceptable for use in support of drug claims.

HiHiker

RECORD OF TELEPHONE CONVERSATION

Date:	July 23, 1999
Project Manager:	Hilfiker
Subject:	Discussion of AE letter comments
NDA:	20-949
Sponsor:	Dey Laboratories
Product Name:	Accuneb (albuterol)
IMTS #:	4551

NDAs 20-949, albuterol sulfate inhalation solution, [redacted] were submitted by Dey Laboratories as 505(b)(2) applications and were issued approvable actions on March 30 [redacted], 1999. The applicant submitted a request for a telephone conference on June 18, 1999, to discuss several of the approvable letter comments. The comments (provided in italics) were extracted from the March 30, 1999, AE letter for albuterol sulfate inhalation solution, and are followed by a summary of the applicant's response and the discussion.

FDA Participants:	David Hilfiker	Project Manager
	Chong-Ho Kim	CMC Reviewer
	Guirag Poochikian	CMC Team Leader
	Vibhakar Shah	CMC Reviewer
Dey Participants:	Partha Banerjee	Product Development
	Peggy Berry, Sr.	Regulatory Affairs
	Roberta Brigida	Regulatory Affairs
	Raj Iyer	Product Development
	Cemal Kemal	Quality Control
	Cal McGoogan	Quality Control

11. The following comments pertain to the drug product specifications.

c. In order to ensure consistent batch to batch quality of the drug product, include particulate matter as a test attribute throughout the shelf life of the drug product, and establish appropriate specifications in terms of the size range of particulate matter as indicated below, based on your data. Additionally, establish an upper range of the particle size.

Particles/container (3 mL)	*Particle size*
NMT — particles	> —
NMT — particles	> —
NMT — particles	> —

The applicant cited USP requirements for small volume injectable products as NMT — particles — and NMT — particles — The applicant asked for the Division's

reference for the specifications cited in comment 11c, and asked why specifications are required for a non-injectable, nebulized drug product.

Dr. Shah stated that the USP proposed specifications for particulates in small volume parenterals are a worst-case scenario. The USP specifications should be the minimum requirement during drug development, but the final specification of a given attribute for a particular product should be data-driven. The specifications that are proposed in the approvable letter are based on the data provided in the NDA submission. Dr. Shah further referred the applicant to the Guidance for Industry regarding Inhalation Solutions as a reference, and reminded the applicant that particulate matter specifications are established and controlled not only at release but also with the stability lots through the shelf-life of the product.

12. The following comments pertain to the drug product test methods.

c. The test method — (vol. 1.2, p. 232) for for albuterol inhalation solution, indicates that it is being used for [ ]. Clarify this discrepancy and revise the method accordingly to be specific for the albuterol sulfate inhalation solution. This revision is also applicable to all QAOPs, MOPs (vol. 1.3, p. 191) and GLPs, as appropriate.

d. The information provided in Method — (vol. 1.2, p. 259) pertaining to a [ ] is not relevant to this NDA and should be deleted. Resubmit an updated method.

e. Provide legible copies of the sampling plans and the sample size codes for QAOP 02-05-007 (vol. 1.3, pp. 132-135).

The applicant proposed continuing use of the current procedure — because of convenience in use and training.

Dr. Shah referred to the method provided on page 232 of NDA 20-949. The method provided in the NDA refers to other products manufactured by Dey Laboratories, such as [ ] but does not refer to albuterol sulfate. Dr. Shah maintained his position that methods provided in the NDA should be specific to the drug product that is the subject of the application.

Dr. Poochikian stated that several products can be included under one method, but that each product should have its own list of steps, especially if the steps are not identical for different products. Dr. Poochikian further stated that the Division is only commenting on the clarity and appearance of the method at this time, and once the applicant submits a revised method, it will be reviewed for content.

Mr. Hilfiker suggested that the company consider revising the method —— to separate the list of steps for each product. That way, several products can remain under one method as long as there is a method specific for albuterol sulfate inhalation solution. Dr. Shah also reminded the company that the methods submitted to NDA 20-949 for products other than albuterol sulfate inhalation solution would not be reviewed. The applicant agreed to revise the protocol as suggested.

14. The following comments pertain to the paper label and components of the paper label

a. To ensure consistent quality of incoming paper label components and the paper label itself, establish appropriate acceptance specifications for extractables/leachables in the solvent and support the specifications with adequate data. Revise the proposed acceptance specifications (vol. 1.4, p. 212)] to reflect the above comment and resubmit an updated version. Additionally, the quality assurance of the paper label may be further supported via submission of a type III DMF for paper labels by The DMF may include quantitative composition and acceptance specifications for each component of the paper label, and release specifications for the paper label.

b. Provide the quantitative chemical composition and identify the supplier/manufacturer of if it contains any additive(s) This information can be provided via authorized DMF reference.

c. Clarify and confirm the chemical names of the components of Provide the quantitative chemical composition of each of the proprietary raw materials if either one or all of them contain more than one chemical compound. Establish and provide appropriate acceptance specifications for these incoming raw materials. In addition, provide the regulatory status with reference to the indirect food additive regulations for the chemical constituent(s) of each component of Alternatively, provide such information for these proprietary raw materials via authorized DMF references.

d. A letter dated January 25, 1999, has been issued to the holder of DMF pertaining to their product

e. *Establish appropriate acceptance specifications supported by adequate data for* [ ] */extractables/leachables for* [ ] *to ensure consistent quality of* — *and its components. (Refer to comment 14a for the paper label.)*

f. *Provide the chemical names/category/class, quantitative composition, acceptance specifications, and regulatory compliance status with reference to indirect food additives regulations (for food contact) for all proprietary components of* [ ] *Additionally, to ensure batch-to-batch consistency in quality, establish and provide appropriate acceptance specifications for the* [ ] *(e.g., specifications for* [ ], *extractable/leachables). Alternatively,* [ ] *may submit this information to the Agency in a type III DMF to ensure consistent quality of* [ ]

g. *Provide the quantitative chemical composition for each of the* [ ] *that are used in various types of inks* [ ] — *(vol. 1.6/pp. 82-84). Provide the regulatory compliance status of each of these components with reference to indirect food additive regulations for its intended use. Additionally, to ensure batch-to-batch consistency in quality, establish and provide appropriate acceptance specifications for inks and their components (e.g., specifications for* [ ] *extractable/leachables). Alternatively,* [ ] *may submit the above information to the Agency in a type III DMF to ensure consistent quality of inks for the paper labels.*

Dey referred to a previous commitment to identify leachables using an [ ] method and [ ] as a [ ] of the drug product. The testing will continue for [ ] However, the applicant wishes to rely on information supplied in a DMF along with stability testing of finished product vials [ ] to address this series of comments.

Dr. Shah first stated that there is currently no DMF submitted from the manufacturer for the finished paper labels. The applicant responded that they are currently working with the manufacturer to put together a DMF for submission. Dr. Shah reminded the applicant that the DMF must qualify each individual component using in the manufacture of the finished paper labels.

The applicant questioned whether these requirements are consistent with the recent Guidance regarding inhalation products. Dr. Poochikian commented that he was partially responsible for

that Guidance, and the Guidance is reflective of the Division's current policies. The Guidance was mainly published to provide industry with a general reference of the ongoing policies. In addition, Dr. Poochikian outlined three major points that the applicant or DMF must supply in regards to extractables and leachables for an inhalation drug product.

1. Provide a quantitative composition of each of the components ([ ]) used in the manufacture of the [ ] paper labels.
2. Identify and establish an extractable profile of the paper label and its components [ ] in [ ] for lot-to-lot quality assurance of incoming paper labels.
3. Identify (if possible) all leachables from the container-closure system (LDPE container and [ ] paper labels) into the drug product and ensure that all leachables are consistent with the composition of the packaging components.

Dr. Poochikian indicated a problem that the applicant will not have knowledge of the material composition of the paper labels if that information is supplied in a DMF, and therefore will not be able to pre-determine the types of compounds to screen in their own stability lots. The applicant acknowledged this difficulty, but stated that they were prepared [ ] based on previous experience. If the manufacturer refuses to conduct adequate leachables and extractables testing and submit that information to the DMF, this is the best that the applicant can do to characterize unknown impurities.

Dr. Shah raised a further concern that the manufacturer may change the composition of the or other materials that are used in the paper labels without Dey's knowledge, and then the screening procedure would no longer be adequate. The applicant acknowledged this problem as well, and stated that they are working closely with the manufacturer to hopefully be able to address these concerns. Dr. Shah stated that the applicant can at least compare the leachables and extractables profiles to ensure batch-to-batch consistency, if they cannot identify the individual impurities. This would at least provide a reasonable assurance that the material composition has not changed.

Dr. Shah also commented that —— may not be [ ] to separate all possible extractable and leachable compounds, and the applicant should consider testing [ ]

23. You have requested specifications — for — impurities in the drug substance,[ ] In order to qualify these impurities, perform a 90 day inhalation study (refer to ICH guideline Q3A). The study should include histopathological evaluation of a complete battery of tissues. It is not necessary for you to perform the study with the isolated impurities, provided that a sufficient margin of safety for the impurities can be demonstrated by using a batch of drug

substance in which they are present. Alternatively, revise the specifications for impurities to [ ]

The applicant stated that the — impurity above has been lowered to [ ] in the drug substance, but that the — impurity [ ] has only been as low as — in the drug substance. The applicant indicated that they could supply data to confirm that several products on the market contained a level of this compound that is equivalent or greater to — The applicant proposed submitting data from marketed products as a response to this comment, and if the Division requests it, the applicant would commit to perform the toxicological tests to qualify this impurity. However, the applicant did not want to hold up the response to the approvable letter to conduct these tests.

Mr. Hilfiker commented that discussions in the Division so far have concluded that the applicant should follow current ICH guidelines that require the toxicological qualification. Therefore, submission of data from marketed products would not be considered a response to this comment. Discussions will continue in regard to this counterproposal, and if our requirements change, the applicant will be notified.

The applicant stated that the Division's deficiency letter to the DMF holder indicated that the manufacturer should reduce this level for [ ] The applicant was receiving a drug substance that contained levels too high for the Division's standards according to the approvable letter. The applicant expressed their annoyance at the Division's discrepancies in the deficiencies communicated to the DMF holder and the deficiencies communicated to them.

Mr. Hilfiker asked which products that Dey has tested to confirm levels of [ ] that are at or above — The applicant replied that Ventolin Inhalation Solution was measured consistently to be [—

The applicant expressed concerns for when further discussions on this matter will conclude, because of the need for them to initiate the toxicology studies if necessary. Mr. Hilfiker stated that further discussions may take place in the next 2 weeks, vacations permitting, and any change in policy would be communicated to the applicant.

David Hilfiker
Project Manager 8/19/99

Cc: Original NDAs 20-949
HFD-570/Division file

HFD-570/Hilfiker
HFD-570/Schumaker/7-27-99
HFD-570/Shah
HFD-570/Kim/8-18-99
HFD-570/Poochikian/8-19-99

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FEB 17 1999

Memorandum

To: NDA 20-949
From: Robin A. Huff, Ph.D., Acting Pharmacology Team Leader /S/ 2-17-99
Date: February 17, 1999
Re: Team Leader NDA Summary

Overall Pharmacology/Toxicology Recommendation - Approvable

Product Summary

— is an inhalation solution of albuterol, a beta-2-agonist, intended for treatment of asthma in patients 6 years of age . — Two solution strengths are proposed for marketing, 0.021 and 0.042%, with a maximum dose of 1.25 qid which equates to 0.1 mg/kg/day for a 50 kg adult and 0.25 mg/kg/day for a 20 kg six year old child. This NDA was a 505(b)(2) application.

Outstanding Issues

Of primary concern is the presence of — impurities in the drug substance, [ ] or (see Dr. Whitehurst's consult dated January 11, 1999). These — impurities should be qualified in a 90-day inhalation study and two genetic toxicology assays, one point mutation test and one chromosomal aberration test (see ICH Q3A Guideline). It should be made clear to the sponsor that the 90-day study should include a histopathological evaluation of a complete battery of tissues because these impurities have not previously been qualified by another route of administration.

Another impurity concern is that [ ] was found to have leached from the overwrap into the drug solution. The sponsor is currently developing an alternative overwrap that will not contain [ ]

In addition to issues of qualifying or removing impurities, several labeling changes should be incorporated. The attached preclinical labeling proposal contains changes made after the initial pharmacology review was finalized. These changes were made in an effort to be consistent with recent revisions to other labels for albuterol products.

Summary of Significant Preclinical Studies

The sponsor did not perform preclinical testing of its own; however, extensive studies have been conducted to support previous approvals of albuterol drug products. As with other beta agonists, cardiotoxicity was the primary toxicity identified in subchronic and chronic studies. Reproductive toxicity studies performed in rats indicated that fertility and peri/post-natal development were unaffected by albuterol treatment. However, albuterol did affect embryofetal development; albuterol was teratogenic in both mice and

rabbits. Albuterol was not genotoxic as assessed in the Ames test, a yeast mutation test, a human lymphocyte clastogenicity test and an *in vivo* mouse micronucleus test. Albuterol was not carcinogenic in an 18 month mouse or 22 month hamster study, but did produce benign leiomyomas in a 24 month rat study. The development of leiomyomas was blocked in a subsequent study by the coadministration of propranolol, a beta antagonist. Data relevant to reproductive toxicity, genotoxicity and carcinogenicity are summarized in product labeling.

cc:
/HFD-570 Division file
/Huff
/Whitehurst
/Hilfiker

CLINICAL PHARMACOLOGY:

Preclinical: Intravenous studies in rats with albuterol sulfate have demonstrated that albuterol crosses the blood-brain barrier and reaches brain concentrations amounting to approximately 5.0% of plasma concentrations. In structures outside the blood-brain barrier (pineal and pituitary glands), albuterol concentrations were found to be 100 times those in 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 are administered concurrently. The clinical significance of these findings is unknown.

PRECAUTIONS:

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 the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 2 times the maximum recommended daily inhalation dose on a mg/m^2 basis). In another study, this effect was blocked by the coadministration of propranolol, a non-selective beta-adrenergic antagonist.

In an 18-month study in CD-1 mice, albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 500 mg/kg (approximately times the maximum recommended daily inhalation dose on a mg/m^2 basis

In a 22-month study in Golden hamsters, albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 50 mg/kg (approximately times the maximum recommended daily inhalation dose on a mg/m^2 basis.

Albuterol sulfate was not mutagenic in the Ames test or a mutation test in yeast. 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 times the maximum recommended daily inhalation dose on a 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 given racemic albuterol sulfate subcutaneously showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg (less than the maximum recommended daily inhalation dose on a mg/m^2 basis)

The drug did not induce cleft palate formation when administered subcutaneously at a dose of 0.025 mg/kg (less than the maximum recommended daily inhalation

dose . — on a mg/m^2 basis). Cleft palate also occurred in — (30.5%) fetuses from females treated subcutaneously with 2.5 mg/kg isoproterenol (positive control).

A reproduction study in Stride — rabbits revealed cranioschisis in 7 of 19 (37%) fetuses when albuterol was administered orally at a dose of 50 mg/kg (approximately — times the maximum recommended daily inhalation dose — on a mg/m^2 basis).

A study in which pregnant rats were dosed with radiolabeled — albuterol sulfate demonstrated that drug-related material is transferred from the maternal circulation 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.

OVERDOSAGE:

The oral median lethal dose of albuterol sulfate in mice is greater than 2000 mg/kg (approximately — times the maximum recommended daily inhalation dose — on a mg/m^2 basis [

]

cc: Original NDA 20-949
HFD-570/Division File
HFD-570/Hilfiker
HFD-570/Whitehurst
HFD-570/Huff

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Steven F. Weinstein, M.D.
17742 Beach Blvd., Suite 310
Huntington Beach, California 92647

FEB 17 1999

Dear Dr. Weinstein:

On November 2-13, 1998, Mr. Ronald L. Koller, representing the Food and Drug Administration (FDA), conducted an inspection of your conduct, as investigator of record, of a clinical study (Protocol No. DL-019) of the investigational drug (albuterol sulfate) Inhalation Solution 0.042% and 0.021% performed for Dey Laboratories. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of these studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we find some deviations from federal regulations and/or good clinical investigational practices. These deviations were detailed on the Form FDA 483 and discussed with you at the close of the inspection. The deviations included your failure to adhere to the protocol by not conducting the ECGs for subjects #821, 824 and 829 and the 4-hour PFT on visit 2 for subject #828. We acknowledge the explanations you provided during the exit interview, and your explanations are part of the inspectional records. We expect, as you stated, that changes will be made in your procedures to assure that deviations like those noted above will not be reported in any of your ongoing or future studies.

We appreciate the cooperation shown Mr. Koller during the inspection.

Sincerely yours,

/S/

Bette L. Barton, [illegible], M.D.
Chief
Clinical Investigations Branch
Division of Scientific
Investigations
Office of Compliance
Center for Drug Evaluation
and Research

cc:
HFA-224
HFD-570 Doc. Rm. NDA 20-949
HFD-570 Review Div. Dir.
HFD-570 MO (O'HEARN)
HFD-570 PM (Hilfiker)
HFD-340/R/F
HFD-344/Chron File
HFD-344/CIB File #9675
HFD-344/CIB REVIEWER (JU)
HFD-344/CIB PM (CURRIER)
HFR-PA250 DIB (KOZICK)
HFR-PA2565 BIMO MONITOR (KOLLER)
HFR-PA2565 FIELD INVESTIGATOR (KOLLER)

CFN: New
Field Classification: VAI
Headquarters Classification:
_____1)NAI
__X__ 2)VAI-no response required
_____3)VAI-response requested
_____4)OAI

If the Field and Headquarters classifications are different, explain why:

Deficiencies noted:
_____ inadequate consent form
_____ inadequate drug accountability
__X__ deviations from protocol
_____ inadequate records
_____ failure to report ADRs
_____ other (specify)

r/d: HWJ:12/11/98
reviewed:BLB:1/7/99
Finaled: 2/4/99 SLK

Note to MO: 19 subjects were enrolled in this study and study records for these 19 subjects were reviewed. No discrepancies between the sponsor supplied Data Listing Tables and the original records were found in the PFTs. Data from this study appear acceptable for use in support of drug claim.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 5, 1999

FROM: H. W. Ju, M.D.

SUBJECT: Final evaluation of clinical investigator inspections.

NDA: 20-949
Sponsor: DEY, L.P.
Drug Product: ~ (albuterol sulfate) Inhalation Solution

TO: Project Manager: David Hilfiker
M.O.: Daniel O'Hearn

SNAME	CITY	ST	ASSIGN	RECD DATE	ACTN DATE	CLASS	REVIEWER
NAYAK	NORMAL	IL	20-OCT-98	25-JAN-99	04-FEB-99	NAI	HWJ
NOONAN	PORTLAND	OR	20-OCT-98	21-DEC-98	07-JAN-99	VAI	HWJ
WEINSTEIN	HUNTINGTON	CA	18-OCT-98	01-DEC-98	04-FEB-99	VAI	HWJ

Key to classifications:

NAI = No deviation from regulations. Data acceptable.
VAI = Minor deviations from regulations. Data acceptable.
OAI = Significant deviations from regulations. Data unreliable.

CC:
HFD-344/Currier
HFD-344/Barton
Original NDA 20-949
HFD-570/Division File
HFD-570/Hilfiker
HFD-570/O'Hearn
HFD-344/Ju

HWJ 2-5-99

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

b/jmc 10-6 R

TO *(Division/Office)*: HFD-530/Boring (LNC)			FROM: HFD-570/Hilfiker (Div. Pulmonary Drug Products)	
DATE: October 6, 1998	IND NO.:	NDA NO.: 20-949	TYPE OF DOCUMENT: Facsimile Correspondence (copy attached)	DATE OF DOCUMENT: September 18, 1998
NAME OF DRUG: Accuneb (albuterol sulfate) Inhalation Solution	PRIORITY CONSIDERATION:		CLASSIFICATION OF DRUG: S	DESIRED COMPLETION DATE: December 1, 1998

NAME OF FIRM: Dey Laboratories, Napa, CA

REASON FOR REQUEST

I. GENERAL

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

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 REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER:

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY 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: Originally proposed tradename, ——— was recommended unacceptable by LNC (consult #1048, completed 9-3-98). Applicant has proposed Accuneb as an alternate name.

cc: Original NDA 20-949
HFD-570/Div. Files
HFD-570/Hilfiker/Shah

SIGNATURE OF REQUESTER: 6-98	METHOD OF DELIVERY (Check one): ☒ MAIL fax 10/6/98 ☐ HAND
SIGNATURE OF RECEIVER:	SIGNATURE OF DELIVERER:

F A X

TRANSMISSION

DEY L.P.
2751 NAPA VALLEY CORPORATE DRIVE
NAPA, CA 94558
TEL: (707) 224-3200
FAX: (707) 224-1364

TO: David Hilfiker

FAX #: 301-827-1271

DATE: 18 September 1998

FROM: Peggy Berry

RE: NDA 20-949

PAGES (including this one): 2

This FAX serves to provide follow-up and updates on several issues as detailed below.

1. Product Names

On 10 September 1998, we discussed a determination made by the FDA nomenclature committee that Dey's selected product names, ——— ; ——— were highly likely to be confused with product names of already marketed products, ——— , respectively.

With this comment, Dey has considered alternate product names and wishes to submit for consideration by the nomenclature committee, the names Accuneb (NDA 20-949) ———

Please let me know as soon as the committee has completed their review. In addition, I would still like to receive information with regard to the members of the committee and, if prepared, a copy of the statement of their determinations.

2. NDA 20-949 Clinical Information Request - Studies DL-009 and DL-019

Our recent amendment completed all requests for clinical information except the hard copy and electronic copy of the DL-009 Efficacy Endpoint Analysis. This information is scheduled to be shipped from Dey to the FDA today.

I have been informed that a new medical reviewer has been assigned to this NDA. Please let me know if Dey can facilitate his review in any way.

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT #	HFD#	PROPOSED PROPRIETARY NAME:	PROPOSED ESTABLISHED NAME:
1048	570	—	Albuterol sulfate inhalation solutions, 0.042/0.021%

ATTENTION: DAVID HILFIKER

A. Look-alike/Sound-alike

	Potential for confusion:		
ACCUTANE	___ Low	XXX Medium	___ High
ACCUPRIL	XXX Low	___ Medium	___ High
OCUFEN	___ Low	XXX Medium	___ High
ATROVENT	___ Low	___ Medium	XXX High
ACCOLATE	XXX Low	___ Medium	___ High

B. Misleading Aspects:

C. Other Concerns:

D. Established Name

XXX Satisfactory

___ Unsatisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations:

___ ACCEPTABLE XXX UNACCEPTABLE

F. Signature of Chair/Date /S/ 9/3/98

RECORD OF TELEPHONE CONVERSATION

Date: August 17, 1998
Project Manager: Hilfiker
Subject: Proposal for Change in Foil Overwrap
NDA: **20-949 and 20-950**
Sponsor: **Dey Laboratories**
Product Name: [redacted]

BACKGROUND:

NDA 20-949 was submitted by Dey Labs on March 27, 1998, for [redacted] (albuterol sulfate) Inhalation Solution. [redacted] A problem identified with [redacted] applications in the pre-NDA phase was the presence of [redacted] appearing as an impurity in the stability samples over time. [redacted]

The applicant proposed a change in the overwrap used for the packaging of both products as a possible solution to eliminate [redacted] (see attached August 3, 1998, fax). A telephone call between the sponsor and FDA was planned to discuss this proposal.

TELECON:

FDA Participants	David Hilfiker, M.S.	Project Manager
	Vibhakar Shah, Ph.D.	CMC Reviewer (NDA 20-949)
	Chong-Ho Kim, Ph.D.	CMC Reviewer (NDA 20-950)
	Guirag Poochikian, Ph.D.	CMC Team Leader
Dey Participants:	Peggy Berry	Regulatory Affairs

(Italicized questions are taken from Dey's proposal (see attached).)

1. *How much stability data is required of the products in the [redacted] overwrap to support approval of the NDA?*

   Dey proposes to conduct stability testing on one lot of [redacted] and on one lot each of [redacted] to support NDA approval. Longer term stability studies of the products in the [redacted] overwrap would be initiated following process validation (currently scheduled for January 1999), using [redacted] lots of each product and strength.

FDA:

a. A minimum of of stability data at both accelerated and long-term storage conditions will be needed for the drug products, packaged in the new overwrap.

b. One lot [ ] can be used in stability studies for NDA approval. Please clarify what types of batches will be used to generate stability samples.

Dey: — batches (approximately — of commercial scale) will be manufactured for stability samples.

c. The proposal to conduct long-term stability studies using — lots of each product and strength following process validation is acceptable. Please clarify the scale of the manufacturing process for lots used in stability protocols.

d. Please clarify which process is scheduled for validation by January 1999.

Dey: The — seal and packaging process will be validated for commercial production by conducting — full commercial runs of each product and strength.

2. *When would the FDA prefer the NDA to be amended to supply information on the overwrap itself and to provide the stability data? Immediately and then following months of stability? Following —months of stability only? Immediately and then upon receipt of request for most recent stability?*

FDA:

a. Please provide a time frame for submission of the — and — months stability data with reference to the user fee goal date of March 30, 1999.

Dey: — months data would be available in December. — months data would be available in March, potentially very close to the user fee goal date.

b. A minimum of 6 months of stability data is required at both accelerated and long-term conditions.

c. The NDA may be amended with the available stability data for the drug product packaged in the proposed — overwrap. However, depending on the timing of the submission of such data with reference to the user fee goal date, FDA may

not be able to review this data prior to taking an action.

3. *Does the FDA have any additional CMC comments at this time?*

FDA:

a. We are concerned about the use of [redacted] paper labels. Likewise, [redacted], one of the components used in the [redacted] may leach into the drug product under normal storage conditions. Have you considered alternative methods to using a paper label, such as [redacted] the vial?

Dey: Yes, we have considered [redacted] The decision to employ a paper label was based on feedback from physicians and consumers who felt that paper labels make the product easier to identify. The possibility of switching to a [redacted] label may be explored.

You may also consider [redacted] the content of the label onto [redacted] at the bottom or top of the vial.

b. For the new overwrap, you should provide the following:

(1) Quantitative composition of the components of the proposed [redacted]

(2) Foil laminate composition of the proposed overwrap.

(3) A side-by-side comparison of the proposed versus the original overwrap foil laminates.

(4) Authorized DMF references for all the components of the container-closure system, as appropriate.

(5) Clarify whether the components of the proposed overwrap comply with the regulations set for the materials that can be used for direct food contact. Provide appropriate CFR references.

(6) Appropriate data to demonstrate the absence of leachables [redacted] from the proposed overwrap into the drug product.

David Hilfiker
Project Manager

8-31-98

Attachment: August 3, 1998, fax

cc: Original NDAs 20-949
HFD-570/Division Files
HFD-570/Hilfiker
HFD-570/Schumaker/8-26-98
HFD-570/Shah/8-27-98
HFD-570/Kim/8-28-98
HFD-570/Poochikian/8-29-98

8-31-98

c:\my_documents\N20949\98-08-17.tel.doc

F A X

TRANSMISSION

DEY L.P.
2751 NAPA VALLEY CORP. DR.
NAPA, CA 94558
TEL: (707) 224-3200 EXT. 475
FAX: (707) 224-0791

TO: Dave Hilfiker

FAX #: 301-827-1271

DATE: 3 August 1998

FROM: Peggy Berry

RE: Question regarding stability NDA 20-949

PAGES (including this one): 1

Comments:

As requested during our telephone conversation today, I am sending you this fax to detail our questions for the chemist regarding the necessary stability for our products if we use a new overwrap foil. Dey currently has [redacted] NDA 20-949 [redacted] vial. The [redacted] vials will be overwrapped with a foil wrapper. The wrapper previously identified by Dey and currently discussed within the NDAs, called [redacted] Dey has provided within the submission all of the necessary toxicology information to indicate that the [redacted] into the vials does not produce a safety concern for the product.

However, in an attempt to improve the situation, Dey has been researching other available overwrap foils. We have now identified a foil, [redacted], which we believe will not allow the [redacted] of this substance and we are confirming through an extractables study that it will not allow the [redacted] of any other substance. Provided that this testing is negative, Dey will proceed to conduct stability studies of our products in the new foil and will amend the NDA application to contain the new overwrap information and the additional stability information.

Regarding the stability information, in the current NDAs, there is up to [redacted] month data available on the unwrapped products and up to [redacted] months data submitted on the products in [redacted] The questions are as follows:

1. How much stability data is required of the products in the — overwrap to support approval of the NDA?

   Dey proposes to conduct stability testing on — lot of — and on — lot each of 0.042% and 0.021% — to support NDA approval. Longer term stability studies of the products in the — overwrap would be initiated following process validation (currently scheduled for January 1999), using lots of each product and strength.

2. When would the FDA prefer the NDA to be amended to supply information on the overwrap itself and to provide the stability data? Immediately and then following months of stability? Following — months of stability only? Immediately and then upon receipt of request for most recent stability?

3. Does the FDA have any additional CMC comments at this time?

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION II

DIVISION OF PULMONARY DRUG PRODUCTS

CDER Pulmonary Group (HFD-155), 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 827-1050 FAX: (301) 827-1271

TO: PEGGY BERRY

Dey Labs

FROM: DAVID HILFIKER

Total number of pages, including cover sheet: 5

Date: 8-31-98

COMMENTS:

official minutes of 8-17-98 telecon.

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

From: **Division of Pulmonary Drug Products**	**HFD-570**
Attention: David Hilfiker	**Phone:** (301) 827-1046
Date: July 8, 1998	
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product	
Proposed Trademark: ———	**NDA/ANDA#** 20-949
Established name, including dosage form: albuterol sulfate inhalation solutions, 0.042/0.021%	
Other trademarks by the same firm for companion products: (none)	
Indications for Use (may be a summary if proposed statement is lengthy): relief of bronchospasm in patients with asthma	
Initial Comments from the submitter (concerns, observations, etc.): (none)	

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

cc: Original 20-949; HFD-570/division file; HFD-570/Hilfiker

APPEARS THIS WAY
ON ORIGINAL

Redacted 1

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

TELECON RECORD

Date:	June 23, 1998
NDA:	20-949
Product:	———
FDA Participants:	J. Lindsay Cobbs, Project Manager Albert Chen, Clinical Pharmacology & Biopharmaceutics Reviewer Ramana Uppoor, Clinical Pharmacology & Biopharmaceutics Team Leader Raymond Miller, OCPB
Sponsor Dey Laboratories:	Peggy Berry, Regulatory Affairs Manager Randy Miller, Director, Product Development

[redacted]

Background: The Agency requested a teleconference with Dey to clarify an information request for additional data/files for review by the Biopharmaceutics reviewer. The following information has been requested.

1. NONMEM control and output files and raw data files in spreadsheet format on diskette.
2. Headings should be provided for raw data files (e.g., age, BW, height, date, dose....) for each column with reference to the volume and page number in the application.
3. Dey agreed to contact the Project Manger Dave Hilfiker in regards to their timeline by the end of next week July 2, 1998, for this submission.

Memorandum of Telephone Facsimile Correspondence

Date: June 26, 1998

To: Peggy Berry,
Regulatory Affairs Manager
(407) 774-0791

From: J. Lindsay Cobbs, R.Ph.
Project Manager

Through: Cathie Schumaker, R.Ph. /S/ for
Chief, Project Management Staff

Subject: Teleconference dated June 23, 1998.

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

A teleconference was held with the Agency on June 23, 1998. A copy of our minutes of that meeting is enclosed. These minutes will serve as the official record of the meeting.

If you have any comments or questions regarding these minutes please call Mr. Lindsay Cobbs, Project Manager, at 301-827-1051.

Thank you.

/S/

J. Lindsay Cobbs, R.Ph.
Project Manager
Division of Pulmonary Drug Products

cc: NDA 20-949
HFD-570/Division File
HFD-570/Cobbs
HFD-570/CHEN
HFD-570/UPPOOR
HFD-570/HILFIKER

DRAFTED BY:LCOBBS/June 26,1998
Initialed by: Uppoor/6-26-98
N:/MY DOCUMENTS/ENDO4-14-98.DOC

H. H. Hilfiker

APR 28 1998

RECORD OF TELEPHONE CONVERSATION

NDA: 20-949 DATE: April 23, 1998

INITIATED BY: __APPLICANT _X__FDA

NAME OF DRUG: (albuterol sulfate) Inhalation Solution

NAME OF SPONSOR: Dey Laboratories

Phone Number: (707) 224-3200 ext. 475
Facsimile (fax) Number: (707) 224-0791

Background: This NDA was submitted for review on March 29, 1998 and received March 30, 1998. The filing meeting was held on April 21, 1998. The reviewers need to request additional information from the sponsor. Therefore a telecon was scheduled.

Present for telecon:
FDA: Dr. Miriam Pina, David Hilfiker, Beverly Gallauresi.
Dey Laboratories: Peggy Berry, Rob Meyers, Roberta Brigida.

Dey Laboratories was requested, and agreed, to submit the following information in an electronic format.

Biopharm:

1. The PD data and NONMEM analysis.

2. The summary section of Item 6., Human Pharmacokinetics and Bioavailability (in Microsoft Word 6.0).

3. The two individual study reports, Nos. DL-009 and DL-010 (in Microsoft Word 6.0).

4. The proposed annotated package insert (3/98 version in Microsoft Word 6.0).

Clinical :

5. The clinical trials reports and protocols for all three major studies.

6. The patients line listings. (An example of the requested electronic submission format was faxed to the sponsor as a reference for an electronic database, preferably in Access.)

Statistics

7. Provide SAS data sets and a list of variables, with a description.

8. Provide Statistical plans for all the pivotal studies.

Chemistry

9. Provide a copy of the stability data (v1.2 p 71-102), particulate matter data (v1.6, p 156-161), indicating the software used (Excel was requested.) Submit updated stability data in electronic form, in addition to the paper copy as they become available.

The following chemistry, controls and manufacturing (CMC) information was also requested.

10. Provide pertinent authorized DMF reference(s) for the components of the [ ] paper label [ ]. Alternatively, provide quantitative composition (with units) for the components of the [ ] paper labels, e.g., [ ] Additionally, provide the composition units (e.g., weight, % w/w etc.) for the constituents of various inks (v1.6, p 83-84). Furthermore, wherever it is applicable, provide appropriate CFR references under which the constituents of all of the paper label components are considered to be safe for use in the packaging components of foods.

Dey's response to # 10:

— - They do not have a DMF reference for the — If not, they will obtain the information (the quantitative composition) from the company.

— - They will check to see if they have a DMF for the — If so, they will obtain LOA's from the company providing the information. If not, they will obtain the information (the quantitative composition) from the company.

Inks - They believe that they have included the list of ingredients and concentration units for the in the current submission. They will locate this information and will

submit the page number reference.

11. Provide a master index of all of the appendices with page numbers submitted to the CMC section, and accompany it with an index of each appendix with page numbers for its contents(topics/reports/methods).

Dey's response to # 11: They will provide a master index of the appendices with page numbers for the entire submission, and will accompany it with an index of each appendix.

Addendum to minutes:
It was noted that the Pharmacology comment was not conveyed to the sponsor during the original telecon. A subsequent telecon was placed to convey this request to the sponsor.

Pharmacology:

12. Provide preclinical/clinical data to support the levels of [redacted] that are proposed for the drug product and drug formulation. Please note that if no preclinical or clinical data are available, preclinical studies may need to be carried out.

/S/

Beverly Gallauresi, R.N., M.P.H.
Project Manager

cc:
Orig.NDA 20-949
HFD-570/Division File
HFD-570/BGallauresi/4-23-98
HFD-570/CSchumaker/4-27-98
HFD-570/DHilfiker/cc only
HFD-570/VShah/4-27-98
HFD-570/MPina/4-29-98
HFD-570/AChen/
HFD-570/VWhitehurst/
HFD-570/GAras/4-29-98

c:n20949.tel1.doc

APR 13 1998

NDA 20-949

Dey Laboratories
2751 Napa Valley Corporate Drive
Napa, CA 94558

Attention: Peggy J. Berry
Regulatory Affairs Project Manager

Dear Ms. Berry:

We have received your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: ——— (albuterol sulfate) Inhalation Solution 0.042% and 0.021%

Therapeutic Classification: Standard

Date of Application: March 27, 1998

Date of Receipt: March 30, 1998

Our Reference Number: 20-949

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on May 30, 1998 in accordance with 21 CFR 314.101(a).

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Should you have any questions, please contact Mr. David Hilfiker, Project Manager at (301) 827-1046.

Sincerely yours,

/S/

Cathie Schumaker
Chief, Project Management Staff
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-949
HFD-570/Div. Files
HFD-570/BGallauresi/4-6-98
HFD-570/CSchumaker/4-7-98
HFD-570/Dhilfiker/
HFD-570/MHimmel/
HFD-570/GPoochikian/
HFD-870/MLChen/
HFD-570/SWilson/
HFD-570/HSheevers/

drafted: bg/April 3, 1998/n:n20949.ack
Final: bg/April 7, 1998
ACKNOWLEDGMENT (AC)

APR 7 1998

Division of Pulmonary Drug Products

ADMINISTRATIVE REVIEW OF NDA

Application Number: NDA 20-949
505(b)(2)

Name of Drug: [redacted] (albuterol sulfate) Inhalation Solutions 0.042% and 0.021%

Sponsor: Dey Laboratories

Indication: For the relief of bronchospasm in patients with asthma (reversible obstructive airway disease) [redacted]
Indicated for pediatric patients between the ages of 2 and 12 years.

Material Reviewed

Submission Date(s): March 27, 1998

Receipt Date: March 30, 1998

Review

Following documents are submitted by the sponsor,

1. FDA form 356h.
2. Form FDA 3397 (User Fee Cover Sheet). User fee paid January 12, 1998, $256,846.
3. Index to the archival copy of the application.
4. Patent Information - No information for this item is being submitted with this NDA.
5. Patent Certification - Included
6. Debarment Certification: Included
7. Application summary - complete
    a. Proposed Text of the Labeling for the Drug Product - Annotated
    b. Pharmacologic Class, Scientific Rationale, Intended Use and Potential Clinical Benefits Summary

c. Foreign Marketing History - not marketed in any other country
d. Chemistry, Manufacturing and Controls Summary
e. Nonclinical Pharmacology and Toxicology Summary
f. Human Pharmacokinetic and Bioavailability Summary
g. Microbiology Summary
h. Clinical Data Summary and Results of Statistical Analysis
I. Benefit/Risk Relationship and Proposed Postmarketing Studies

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Conclusions:

This application is considered fileable from an administrative perspective.

/S/

Beverly Gallauresi
Project Manager

cc:
Original NDA 20-949
HFD-570/Division file
HFD-570/CSchumaker/
HFD-570/BGallauresi/ 4/1/98
draftted: bg/4-1-98

c:\n20949.ar

Printed by Beverly Gallauresi

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 06-Apr-1998 01:36pm
From: Mei-Ling Chen
CHENME
Dept: HFD-870 PKLN 13B17
Tel No: 301-443-1640 FAX 301-480-6645

Subject: NDA 20-949 - ——— (albuterol sulfate) Inhalation Sol.

Beverly:

Albert (Tien-Mien) Chen will be the reviewer for this NDA.

Sorry for the delay in responding to you.

Mei-Ling

NDA # [illegible] DOCUMENT ID/LETTER DATE _____

APPLICANT NAME DEY LABS

PRODUCT NAME (ALBUTEROL SULFATE) INHALATION SO

FORM MUST BE COMPLETED ASAP

1. (YES) User Fee Cover Sheet Validated?

NOTE TO DOCUMENT ROOM:
PLEASE MAKE THE FOLLOWING CHANGES TO THE CDMIS DATA ELEMENTS

2. (YES) NO CLINICAL DATA?
[Check YES if contains study reports or literature reports of what are explicitly or implicitly represented by the applicant to be adequate and well-controlled trials. "Clinical data do not include data used to modify the labelling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling).]

REF IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE *CROSS REFERENCED* IN ANOTHER SUBMISSION?

3. YES (NO) NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (OTHER THAN BUNDLING)? IF YES, list ALL NDA numbers, review divisions & indicate those for which application fees apply.

NDA #	DIVISION		
N_____	_____	FEE	NO FEE
N_____	_____	FEE	NO FEE

4. (YES) NO BUNDLING POLICY APPLIED CORRECTLY? NO DATA ENTRY REQUIRED FOR ELEMENT
[Check YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Check NO if application should be split into more than one application or submitted as an original instead of a supplement. IF NO, list resulting NDA numbers, and review divisions.]

NDA #	DIVISION	NDA #	DIVISION
N_____	_____	N_____	_____

5. P (S) PRIORITY OR STANDARD?

/S/ _____ /S/ 4/6/98

6. CSO SIGNATURE/DATE SCSO CONCURRENCE SIGNATURE/DATE

COPY DISTRIBUTION: ORIGINAL TO ARCHIVAL AFTER DATA ENTRY, ONE COPY EACH TO DIVISION FILE AND CDER, ASSOCIATE DIRECTOR FOR POLICY HFD-5

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

Form Approved: OMB No. 0910-0297
Expiration Date: November 30, 1996

USER FEE COVER SHEET

See Instructions on Reverse Before Completing This Form.

1. APPLICANT'S NAME AND ADDRESS

Dey Laboratories
2751 Napa Valley Corporate Drive
Napa, CA 94558

2. USER FEE BILLING NAME, ADDRESS, AND CONTACT

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

3. TELEPHONE NUMBER *(Include Area Code)*
(707) 224-3200

4. PRODUCT NAME
Albuterol Sulfate 0.021% and 0.042%

5. DOES THIS APPLICATION CONTAIN CLINICAL DATA? ☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

6. USER FEE I.D. NUMBER
3375

7. LICENSE NUMBER/NDA NUMBER
N 20-949

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED BEFORE 9/1/92

☐ THE APPLICATION IS SUBMITTED UNDER 505(b)(2) *(See reverse before checking box.)*

☐ AN INSULIN PRODUCT SUBMITTED UNDER 506

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGIC PRODUCT LICENSED UNDER 351 OF THE PHS ACT

9.a. HAS THIS APPLICATION QUALIFIED FOR A SMALL BUSINESS EXEMPTION? ☐ YES ☒ NO *(See reverse if answered YES)*

b. HAS A WAIVER OF APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO *(See reverse if answered YES)*

This completed form must be signed and accompany each new drug or biologic product, original or supplement.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Peggy J. Berry	Regulatory Affairs Project Manager	12/5/97

FORM FDA 3397(3/95)

Redacted 1

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

RECORD OF TELEPHONE CONVERSATION

IMTS #: 1950
IND: [redacted] 44,281 DATE: November 17, 1997
SPONSOR: Dey Laboratories
DRUG(S): [redacted]
Albuterol Pediatric Inhalation Solution
INITIATED BY: DEY Laboratories
NAMES AND TITLES OF PERSONS WITH WHOM CONVERSATION WAS HELD:

Dey Laboratories: Ms. Peggy Berry, Ms. Roberta Brigida, Ms. Antoinette Douglas, Dr. Raj Iyer, Dr. Allan S. Kaplan, Dr. Cemal Kemal, and Dr. Rob Myers

[

]

FDA: Dr. Chong-Ho Kim, Dr. Linda Ng, Dr.Guirag Poochikian, and Ms. Denise Toyer

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BACKGROUND

See submissions dated: September 12 and 29, 1997, October 22, 1997 and facsimile dated November 7, 1997. A preNDA CMC meeting was held on August 8, 1997. Dey submitted a chemistry information amendment which includes protocols for the leachables and extractables; the stability data on the overwrapped product; and a proposal for [ ] testing.

TELECON

The sponsor stated that their plan is to submit the pediatric albuterol NDA during the second week of December 1997 [

]

The discussion started with the protocols in the September 12, 1997 submission and then proceeded to the November 7, 1997 facsimile.

Technical protocol Page 18-00010

- This is a one-time protocol. Dey's vendors are required to notify Dey in advance of any changes in

materials which they provide. If a vendor changes any part of their supplies Dey will then conduct a new protocol.

- The methods for this protocol have not been validated at this time. Dey is currently working with contractors to develop these methods.
- At the time of submission Dey will have approximately months long term stability data and months accelerated data.

Division:

Sponsor should use validated methods that have the sensitivity to detect impurities. Standards should be used for quantitation. The composition and profile of each of the materials should be submitted.

Testing should be performed up to months for accelerated and through expiry for the drug product. We also recommend that an assay of the actual drug product solution at expiry for leachables be included. Actual values should be reported.

Technical protocol Page 18-00013

- [ ]

Division:

Exclusion of — (section 5.8) is not acceptable. The criteria and test method for — must be clearly stated as part of the protocol. The Division recommends conducting an — test

Technical protocol Page 18-00016

- There may be differences between the testing procedures and the actual process for making the vial (e.g., duration, time, temperature, etc.). The sponsor will use vials for testing in section 4.21.
- The sponsor has no plans, at the current time, to conduct these tests on all batches. (The extractables/leachables testing will be conducted on empty vials.)

- Acceptance tests may be conducted on the pellets. All incoming batches will have USP testing

Division:

Extractable testing for acceptance of pellets is recommended. The [ ] instructions seem excessive, even though they may be indicative of the U.S.P. recommendations. The sponsor proposed omitting the [ ] which is acceptable to the Division. Actual values should be reported.

Stability Report Page 18-00019, 18-00020, 18-00021

- The [ ] test method has been validated. The stability reports only list The values have been in the [ ] units range for — months. Dey would like to reduce the specification to less than — units.
- The percentage of label claim is based on mg/mL. The Division's recommendations from the August 8, 1997 meeting will be instituted at the next stability point. Dey plans to convert the specification to "per vial."

Division:

The validation method with the data for the [ ] test should be submitted to the Division. The sponsor should re-evaluate the method for quantitation/detection limit. This qualitative test should be able to discern lower values than were specified in the protocol.

The [ ] test can be omitted if the data generated from this test can be obtained from other tests that are being conducted.

The data should be reported both for the individual and total. The specifications should be re-evaluated and revised to reflect the actual data.

Comments on specification will be deferred until actual data are submitted.

Testing

- Dey will use the [ ] to conduct this test. Testing will be monitored initially and at expiry.

Division:

More than — lots are needed before this specification can be eliminated. Dey could submit the data for the — lots with the NDA. Once the product is approved, it is likely that the Division would require a Phase 4 commitment for release testing on post-production lots. The data would need to be reviewed by the Division prior to eliminating this test. The specification should cover ranges.

November 7, 1997 Facsimile

- Dey has decided to use the overwrap which was used in their testing. The overwrap testing was conducted on Dey's product which was [ ] These assays were conducted during the latter part of October. (See table one.) Dey feels that the levels they want to use are substantially below the levels which are safe in humans. **Post Meeting Note: The data listed below were verified with Dr. Fordyce on December 5, 1997.**

Table One.

Product	Assay Conducted	expiration date of sample	ppm
—	Dey QC (ambient conditions)	2/97	—
—	Dey QC (ambient conditions)	10/98	—
—	Dey R&D	10/98	—

Division:

The sponsor should submit the pharmacology and toxicology information to support their position on the [ ] consults, articles, etc.) We will reply to Dey's proposal as soon as our pharmacology and toxicology reviewers have had an opportunity to review the information.

Denise P. Toyer, R.Ph.
Project Manager

Memorandum of Telephone Facsimile Correspondence

Date: December 9, 1997

To: [redacted] Ph.D.
[redacted] for Dey Laboratories

[redacted] Ph.D.
[redacted] for Dey Laboratories

From: Denise P. Toyer, R.Ph.
Project Manager

Subject: Minutes for Meeting

Reference is made to the November 17, 1997, telecon held between representatives of your company and members of this division. Attached is a copy of our final minutes for that meeting. These minutes will serve as the official record of the meeting/telecon. If you have any questions or comments regarding the minutes, please call me at 301-827-5584.

Thank you.

/S/

Denise P. Toyer
Project Manager
Division of Pulmonary Drug Products

cc: Original IND
HFD-570/Division File
HFD-570/Kim/11-25-97
HFD-570/Ng/11-26-97
HFD-570/Poochkian/12-2-97
HFD-570/Jani
HFD-570/Toyer

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Meeting Date: August 11, 1997
Location: Parklawn bldg. conf rm "L"
Time: 1:30-3:00 PM
Sponsor: Dey Labs
IND: 44,281/Albuterol Inh Sol
Type of Meeting: Pre-NDA

IMTS # 1125

FDA Attendees:

Girish Aras, Ph.D.	Statistician
Dale Conner, Ph.D.	Clinical Pharmacology, Team Leader
Parinda Jani	Project Manager
John K. Jenkins, M.D.	Division Director
Chong Ho Kim, Ph.D.	Chemistry Reviewer
Robert Meyer, M.D.	Medical Officer, Team Leader
Babatunde Otulana, M.D.	Medical Officer
Guirag Poochikian, Ph.D.	Chemistry, Team Leader
Hilary Sheevers, Ph.D.	Pharmacologist, Team Leader
Virgil Whitehurst, Ph.D.	Pharmacology Reviewer
Steve Wilson, Ph.D.	Statistician, Team leader

Dey Lab Attendees:

Allan Kaplan, Ph.D.	Vice President, Technical Affairs
Randy Miller, Ph.D.	Director, Product Development
[ ]	Medical Consultant

[ ] **Attendees**:

[ ]	Senior Vice President, Medical Affairs
	Medical Director
	Medical Writer
	Biostatistician
[ ]	Executive Director, Regulatory and Product Development

Background: See the submission dated July 14, 1997

Dey Labs presented an overview of the planned NDA submission. The goals for the meeting were to determine the dose requirements and also to determine whether exclusivity would be granted to this product.

Pharm/Tox

Dr. Whitehurst said that the NDA should contain an extensive literature review of animal studies. The latest information from the literature should be used in the labeling. The animal species, dose used, and the duration of the dosing should be identified and included in the NDA.

Pharmacokinetics

Dr. Conner said that Item 6 of the NDA should contain a complete literature review and summary of the pharmacokinetics studies. The clinical pharmacokinetics study that Dey Lab has conducted should also be included in Item 6.

Clinical

The clinical section of the NDA will contain 3 pediatric studies, DL-009, DL-010 and DL-019. The NDA will be submitted for 1.25 mg and 0.625 mg strengths for children 6 years and above. Dey Labs ANDA for 0.083% albuterol sulfate solution (2.5 mg/0.083%) was approved in 1992. Currently, albuterol inhalation solution is not available in 1.25 mg or 0.625 mg unit dose vials. Dey Lab understands that Ventolin Inhalation Solution was recently approved for age 2 years and above, and the ANDA labeling will have to be identical to the approved Ventolin Labeling.

The following clinical issues were discussed. Industry questions are in bold.

1. **The results of the Pediatric study suggest that both doses of the inhalation solutions were equally effective. However, some children in clinical situations may require the higher concentrations (1.50 mg) we plan to offer both the .75 mg and 1.5 mg solutions for marketing. Is this acceptable?**

   Dey Lab should provide justification for potential need for higher dose. The proposed age group breakdown, i.e., 9-12 years and 6-8 years, for the to-be-marketed doses is a review issue.

2. **We have included in our statistical analysis of study DL-019, subgroup analysis based on the factors of age, race, severity of illness, and corticosteroid use. Are there any additional analysis which the Division might contemplate?**

Additional subgroup analysis by gender and weight, along with the required standard analysis, should be submitted.

3. **Is the plan for the ISS and ISE acceptable?**

The proposed analysis plans for the ISS and ISE are acceptable.

4. **We plan to include in the ISS a review of the pediatric literature on nebulized albuterol, but limit our review to the published literature since 1990, Is this acceptable?**

Dey Labs may need to conduct literature search beyond 1990 to support the indication for other age groups. The search strategies should be described in the NDA. The source of the database used should be identified.

Chemistry, Manufacturing and Controls (CMC)

Dey Labs is planning to submit an official response to the deficiencies letter dated March 10, 1994, before filing the NDA. The product will be marketed with an overwrap. The extractables data will be included in the NDA.

The following agreements were made.

1. An extractables study with more [redacted] will be required.

2. A study for water loss at 40°C/20%RH will be required. This is the modification that the Agency recommends to the ICH guidelines.

3. A quality control test for incoming material as recommended by USP (attributes) will be required.

4. A complete profile of individual and total impurities for the drug substance and the drug product must be submitted. Each individual impurity for the drug substance should be identified and qualified. Each impurity for the drug product should be specified and qualified.

5. Dey Lab will submit the protocol for the extractables/leachables study. Once the protocol is reviewed, a telecon may be held if necessary.

6. Photostability data will be required to determine the labeling of the product once the overwrap is removed.

7. The method for determining foreign particulates in the drug product (— formulation) should be validated.

8. — -months supportive stability data for the overwrapped and — -months data for the non-overwrapped product at the time of submitting an NDA will be acceptable. Additional data should be submitted during the review process.

Exclusivity

Dr. Jenkins said that exclusivity is not granted until a product is approved. It cannot be guaranteed up-front at the time of an NDA submission as this is a review issue. Dey Labs is proposing different doses for different age groups. There is a question as to whether the clinical trial was required, as the literature data could have supported the doses. The dosage form will be a more convenient way to administer the drug, but this may not be the reason exclusivity could be granted. Dey Lab feels that the formulation is different, — and that should be considered for granting the exclusivity. Dr. Jenkins responded that change in formulation does not make it a new product. Also, filing an NDA does not make a sponsor automatically eligible for an exclusivity designation for the product.

Dr. Jenkins said that the exclusivity issue will be discussed internally and then will be discussed with the Dey Lab.

/S/

Parinda Jani

Project Manager

CC:
ORIG IND 44,281
DIV FILE/HFD-570
HFD-570/OTULANA/9-10-97
HFD-570/MEYER/9-10-97
HFD-570/WHITEHURST/9-11-97
HFD-570/SHEEVERS/9-12-97
HFD-570/CONNER/9-15-97
HFD-570/ARAS/9-15-97
HFD-570/WILSON/9-15-97
HFD-570/KIM/9-15-97
HFD-570/POOCHIKIAN/9-15-97
HFD-570/SCHUMAKER/9-9-97
HFD-570/JANI/9-8-97

Division/Office): HFD-530 (Boring)			FROM: HFD-570 (Hilfiker)	
E 7-8-98	IND NO.	NDA NO. 20-949	TYPE OF DOCUMENT Trademark Review Request	DATE OF DOCUMENT 7-8-98
OF DRUG —	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE

IE OF FIRM:

REASON FOR REQUEST

I. GENERAL

EW PROTOCOL
ROGRESS REPORT
EW CORRESPONDENCE
RUG ADVERTISING
DVERSE REACTION REPORT
ANUFACTURING CHANGE/ADDITION
EETING PLANNED BY

☐ PRE–NDA MEETING
☐ END OF PHASE II MEETING
☐ RESUBMISSION
☐ SAFETY/EFFICACY
☐ PAPER NDA
☐ CONTROL SUPPLEMENT

☐ RESPONSE TO DEFICIENCY LETTER
☐ FINAL PRINTED LABELING
☐ LABELING REVISION
☐ ORIGINAL NEW CORRESPONDENCE
☐ FORMULATIVE REVIEW
☒ OTHER *(SPECIFY BELOW)*:
Attached Trademark

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
YPE A OR B NDA REVIEW ND OF PHASE II MEETING ONTROLLED STUDIES ROTOCOL REVIEW THER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

OLUTION
VAILABILTY STUDIES
ASE IV STUDIES

☐ DEFICIENCY LETTER RESPONSE
☐ PROTOCOL-BIOPHARMACEUTICS
☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

HASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
RUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
ASE REPORTS OF SPECIFIC REACTIONS (List below)
OMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ SUMMARY OF ADVERSE EXPERIENCE
☐ POISION RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

MMENTS/SPECIAL INSTRUCTIONS:

GNATURE OF REQUESTER — 7-8-98	METHOD OF DELIVERY (Check one) ☒ MAIL ☐ HAND
GNATURE OF RECEIVER	SIGNATURE OF DELIVERER

cc: Orig NDA 20-949
HFD-570/division file
HFD-570/Hilfiker
HFD-570/Schumaker

7/9/98