

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
20950

CORRESPONDENCE

141/12/98

NDA 20-950

JUN 18 1998

Dey Laboratories
2751 Napa Valley Corporate Drive
Napa, CA 94558

Attention: Peggy J. Berry
Regulatory Affairs Manager

Dear Ms. Berry:

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

Name of Drug Product: Duivent (albuterol sulfate and ipratropium bromide) Inhalation Solution, 0.083% and 0.017% respectively

Therapeutic Classification: Standard (S)

Date of Application: May 28, 1998

Date of Receipt: May 29, 1998

Our Reference Number: 20-950

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 July 27, 1998, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be May 29, 1999.

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

NDA 20-957
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If you have any questions, contact Mr. David Hilfiker, Project Manager, at (301) 827-1046.

Sincerely yours,

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

Hilfiker

JAN - 4 2000

NDA 20-950

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 2, 1999, of your November 29, 1999, resubmission to your new drug application (NDA) for Duoneb (albuterol sulfate, 3.0 mg, and ipratropium bromide, 0.5 mg, per 3 mL vial) Inhalation Solution.

This resubmission contains additional information submitted in response to our May 28, 1999, action letter.

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

CSO
P. 10/27

NDA 20-950

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

OCT 30 2000

Attention: Peggy J. Berry
Regulatory Affairs Manager

Dear Ms. Berry:

We acknowledge receipt on September 21, 2000, of your September 19, 2000, resubmission to your new drug application (NDA) for DuoNeb (2.5 mg albuterol sulfate and 0.5 mg ipratropium bromide) Inhalation Solution.

This resubmission contains additional information submitted in response to our June 2, 2000, action letter.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is March 21, 2001.

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

Sincerely yours,

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



DUPLICATE

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DEY, L.P.
2751 Napa Valley Corporate Drive
Napa, CA 94558
TEL. (707) 224-3200 FAX (707) 224-1364

09 March 2001



Robert J. Meyer, M.D., Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation Research
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-950 A-023
DuoNeb™ (albuterol sulfate/ipratropium bromide) Inhalation Solution
CMC Amendment: Request for Information

Dear Dr. Meyer:

This letter is sent in response to the FDA's communication dated 08 March 2001, regarding NDA 20-950, DuoNeb. The FDA's comments are repeated in bold below followed by Dey's response.

1. **You are reminded of your commitment to conduct a 90-day inhalation toxicology study to qualify impurity. The results will be submitted as a Phase 4 Commitment within 12 months of approval. [Comment 1.a]**

Dey commits to conducting a 90-day inhalation toxicology study to qualify impurity. The results will be submitted as a Phase 4 Commitment within 12 months of approval.

2. **You are reminded of your commitment to monitor leachables throughout the shelf-life of the drug product during the long term stability of the first three production batches. This test should be continued if an appropriate relationship is not established between extractables and leachables. [Comment 9.a]**

Dey commits to monitoring leachables throughout the shelf-life of the drug product during long-term stability of the first three production batches. This test will continue to be conducted if an appropriate relationship is not established between extractables and leachables.

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3. **Raw material specification for "Pouch Foil Laminates for unit dose products" page 2-234, amendment dated September 19, 2000) contains inaccurate information. Revise the specification and submit the revised version. [Comment 9.d]**

The raw material specification for "Pouch Foil Laminates for Unit Dose Products" has been revised. The inaccurate information has been removed and the specification now includes only foil laminate. The revised specification is attached (Attachment A).

4. **The following comments pertain to foreign particulates [Comment 11.a]:**

- a) **Since the container/closure system is the same, foreign particulates specifications for the DuoNeb should be identical to those for the AccuNeb. Justify/explain the discrepancy.**

Since the container closure system is the same, the DuoNeb specification, based upon the FDA comments, was revised to be identical to the AccuNeb specification. A revised finished product specification is attached (Attachment B).

- b) **Provide a commitment to monitor foreign particulates through the shelf-life of the drug product, to tighten the proposed acceptance criteria with additional data, and to submit a supplement within a reasonable period of time.**

Dey will monitor foreign particulates through the shelf-life of the drug product, will tighten the proposed acceptance criteria with additional data, and will submit a supplement within 12 months of approval.

- c) **The updated stability data of the lots R301 and R324, made with overwrap, indicate that the lots failed to meet "the particulate matter specification" even at time 0. Explain the cause(s) of failure. State the nature of particulate.**

Dey has performed analysis to determine the nature of particulates observed. The majority (approximately 60%) of the particulates are silicates, which are found on the resin used to make the polyethylene vials. Most of the remaining (approximately 30%) of the particulates, upon filtration, appear to be sodium chloride, which is an inherent component of the drug solution.

Since the majority of the particulates are inherent in the resin, Dey is working with the resin vendor to identify ways to reduce the silicates. Silicates come from the environment where the resin is manufactured (*i.e.*, sand). Experimental data, to date, shows that if the resin is handled and packaged differently than the current process used by the vendor, the product will meet the proposed specification.

5. The following comments pertain to the stability protocol. [Comment 12]

- a) Revise the sampling plan, specifically pertaining to “Annual Reserve Batches” (9.4, page 2-298)**

References to “Annual Reserve Batches” do not pertain to stability testing and have been removed from the stability protocol. The sampling plan has been revised to clarify that sections 9.1 and 9.2 reflect the stability commitment. Specifically Dey commits to performing annual stability studies on 2% of the batches produced yearly, but not less than 3 total batches per year.

- b) Incorporate the following statements into the stability commitment section:**

- i) Conduct and/or complete the necessary studies on three 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.**
- ii) Submit cumulative stability study results on commitment and annual batches in the annual report.**
- iii) 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).**

The stability protocol has been revised to incorporate statements i, ii, and iii.

09 March 2001
Dr. Meyer
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- c) **Provide an updated stability protocol and data that reflect all requested modifications.**

The updated stability protocol, with all requested modifications, is located in Attachment C.

6. **The following comments pertain to the labeling:**

- a) **The ingredient name for albuterol should be changed to "3.0 mg albuterol sulfate" wherever applicable. Submit revised labels for the package insert, overwrap pouch, and carton.**

All labeling pieces were modified to change the albuterol ingredient name to "3.0 mg albuterol sulfate." A revised package insert, overwrap pouch label, and carton are located in Attachment D.

- b) **Add the following statement to the foil pouch labels:**

Unit-dose vials should remain stored in the protective foil pouch at all times. Once removed from the foil pouch, the individual vials should be used within one week. Discard if the solution is not colorless.

The specified statement has been added to the foil pouch label. Please note that the addition of this text necessitated the slight rearrangement of other text on the label. None of the text previously submitted changed or reduced in size. The revised overwrap pouch label is located in Appendix D.

- c) **The embossing artwork [Fax dated February 28, 2001] is acceptable. Provide actual product samples as soon as possible.**

Dey will provide the FDA with 5 vials (1 card) of actual product samples from the first commercial batch of DuoNeb.

If you have questions or need additional information, please contact me at 707-224-3200, x4750 or 707-333-8408.

Sincerely,


Peggy J. Berry
Director, Regulatory Affairs

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