CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20950

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-950

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

Attention: Peggy J. Berry
Director
Regulatory Affairs

Dear Ms. Berry:

Please refer to your new drug application (NDA) dated May 28, 1998, received May 29, 1998, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for DuoNeb (3.0 mg albuterol sulfate and 0.5 mg ipratropium bromide per 3 mL) Inhalation Solution.

We acknowledge receipt of your submissions dated July 2 and August 26, 1998, and February 11, March 15 and 26, and November 29, 1999, and January 20, September 19, October 23, November 10, and December 6 and 12, 2000, and February 14, 15, 22, 23, 27, and 28, and March 1, 6, 7, 8, 9, 13, 15, 16, and 19, 2001. Your submission of September 19, 2000, constituted a complete response to our June 2, 2000, action letter.

This new drug application provides for the use of DuoNeb (3.0 mg albuterol sulfate and 0.5 mg ipratropium bromide per 3 mL) Inhalation Solution for the treatment of bronchospasm associated with COPD for patients who require more than one bronchodilator.

We have completed the review of this application, as amended, and it is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted March 16, 2001, vial labeling submitted March 9, 2001, protective foil overwrap label submitted March 16, 2001, and carton labels submitted March 16, 2001). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 20-950." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your agreement to monitor leachable compounds through the expiry period of the product for the first three commercial batches to be placed in your long-term stability program. If you are not able to correlate the leachable compounds profile to the existing extractable compounds profile after analysis of the first three commercial batches, further monitoring may be necessary.

We remind you of your postmarketing study commitments in your submission dated March 9, 2001. These commitments are listed below.

1. Conduct a 90-day inhalation toxicology study in one rodent and one non-rodent species to qualify the bis-ether albuterol impurity.

   Final Report Submission: Within 12 months of the date of this letter

2. Conduct a study to identify and quantitate foreign particulates through the shelf-life of the drug product. Submit a prior approval supplement to tighten (as appropriate) the proposed acceptance criteria based on these data.

   Final Report Submission: Within 12 months of the date of this letter

Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "Postmarketing Study Final Report" or "Postmarketing Study Correspondence."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving the pediatric study requirement for the use of DuoNeb (3.0 mg albuterol sulfate and 0.5 mg ipratropium bromide per 3 mL) Inhalation Solution for the treatment of bronchospasm associated with COPD for patients who require more than one bronchodilator, because this disease does not substantially affect pediatric populations.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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

Sincerely yours,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

/s/

Robert Meyer
3/21/01 04:38:28 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20950

APPROVABLE LETTER

Hi File.

MAY 28 1999

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:

Please refer to your new drug application (NDA) dated May 28, 1998, received May 29, 1998, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Duoneb (albuterol sulfate, 3.0 mg, and ipratropium bromide, 0.5 mg) inhalation solution.

We acknowledge receipt of your submissions dated July 2 and August 26, 1998, and February 11, March 15, and March 26, 1999.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to adequately address the following comments and requests.

1. Respond to comments 1–9 listed in the deficiency letter dated March 30, 1999, that pertain to the drug substance, albuterol sulfate, for NDA 20-949 (albuterol sulfate inhalation solution).

2. The following comments pertain to the drug substance, ipratropium bromide.

   a. Provide specifications and test methods for alcohol

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10. The following comments pertain to the clinical data reviewed for this application.

    a. There appears to be an interaction of adverse event reporting with disease severity. Using the same baseline indices of severity as before (using albuterol and ipratropium prescription cotherapy), analyze the distribution of adverse event types by two-category severity. Refer to volume 23, pages 147-8 of the original NDA submission.

    b. The narrative summaries of deaths, discontinuations and serious adverse events included more detailed information than was to be found in the case report forms. This raises the possibility of additional information sources of important safety data to which we did not have access. Provide information on how these detailed narratives were constructed.

    c. We are concerned that the large number of drop-outs observed in Study DL-024 may have had a serious effect on the reported results. Discuss the sensitivity of the results to the effect of drop-outs and the potential impact of missing data on the analyses.

    d. Analyze the first period of the cross-over phase of Study DL-024, examining treatment differences for this period as if the trial had been designed as a parallel group study.

In addition, it will be necessary for you to submit draft labeling revised as follows. These labeling comments are preliminary. Further labeling comments will be provided once you have addressed the deficiencies outlined in this letter.

11. The following comments pertain to the CLINICAL PHARMACOLOGY section of the package insert.

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Proposed Labeling

If new information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

You are advised to contact the division regarding the extent and format of your safety update prior to responding to this letter.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely yours,

Robert J. Meyer, M.D.
Acting Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Hilliker

NDA 20-950

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

JUN 2 2000

Attention: Peggy Berry
Director
Regulatory Affairs

Dear Ms. Berry:

Please refer to your new drug application (NDA) dated May 28, 1998, received May 29, 1998, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for DuoNeb (3.0 mg albuterol sulfate/0.5 mg ipratropium bromide per 3 ml) Inhalation Solution.

We acknowledge receipt of your submissions dated November 29, 1999, and January 20, 2000. Your submission of November 29, 1999, constituted a complete response to our May 28, 1999, action letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following comments. Note that the cited comments in parentheses refer to comments in our May 28, 1999, action letter.

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

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In addition, it will be necessary for you to submit draft labeling revised as in the enclosed marked-up draft labeling. Additional labeling comments will be forthcoming when the above issues have been adequately addressed.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

You are advised to contact the Division regarding the extent and format of your safety update prior to responding to this letter.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely yours,

/S/

Robert J. Meyer, M.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure