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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-949

Approvable Letter (S)

NDA 20-949

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

JUN 6 2000

Attention: Peggy Berry
Director
Regulatory Affairs

Dear Ms. Berry:

Please refer to your new drug application (NDA) dated March 27, 1998, received March 30, 1998, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for AccuNeb (0.63 mg and 1.25 mg albuterol sulfate per 3 mL) Inhalation Solution.

We acknowledge receipt of your submissions March 29 and December 3, 1999, and January 20, February 22, April 21, and May 19, 2000. Your submission of December 3, 1999, constituted a complete response to our March 30, 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 March 30, 1999, action letter.

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

   a. The specification [ ] proposed for the [ ] in the drug substance cannot be finalized until it is qualified at an appropriate level. Refer to comment 12 of this letter for further information on qualification. (comment 2.a.)

   b. Tighten the proposed pH specification to reflect the pH values obtained for the batches of the drug substance used in the primary stability batches of the drug product. (comment 2.f.)

   c. Delete the phrase [ ] ' used for equipment and reagents, if not validated for their intended purpose, in all methods (Vol. 5: — , p. 0019; — , p. 0155 — , p. 0162 and — p. 0136). This comment is applicable to all analytical methods that are used for the drug substance and drug product (comment 4.e.).

d. Although [ ] is regarded as a process impurity, it is also a potential degradation product. Revise method — to resolve the separation of [ ] 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 — and — and provide the data to ensure that the formation of [ ] does not increase with time and that it remains below the proposed specification, [ ] [ ] If the data prove unequivocally that [ ] is not formed or increased with storage, method — may be used as is. Alternatively, adopt methods — and — for the quantitation of impurities/degradation products in the albuterol sulfate inhalation solution. (comment 4.b.)

e. With reference to the chromatogram provided with method specify [ ] prior to [ ] and the unresolved [ ] [ ] with [ ] (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 [ ] [ ] (comment 5.d.)

f. The stability protocol for the drug substance does not address any commitment for stability testing of the annual batches of the drug substance, albuterol sulfate. Revise the stability protocol to address this concern. Additionally, indicate who will perform the stability testing of the annual batches of the drug substance. Note that the number of batches that need to be placed on annual stability testing should be reflective of the number of batches produced per year. Rectify the discrepancies noted with the proposed specifications for [ ] and total impurities, submitted within the stability protocol and in document — (p. 5 0247/Vol. 5). Resubmit the revised stability protocol to reflect the above changes. (comment 9)

2. The following comments pertain to the proposed specifications for the drug product, albuterol sulfate inhalation solution.

a. The proposed specification, [ ] and [ ] is not reflective of the [ ] stability-data provided on [ ] lots with the original overwrap, TRP — (Vol. 3: pp. 0176-0216, 0224, 0228) and [ ] data provided on [ ] lots with the new overwrap, SOP — (Vol. 3: pp. 0239, 0243, 0244). Tighten the specifications for both [ ] to reflect the data (e.g., [ ]. Resubmit revised drug product specifications that reflect the above changes.

(comments 11.a.(3) and 20.c.)

b. Based on the room temperature data submitted for total impurities in the drug product, the proposed specification, [ ] for total impurities in the drug product is not justified (Vol. 3: pp. 0193-0216). Reduce the proposed specification for total impurities in the drug product. (comments 11.a.(1) and 20.c.)

c. Revise the lower value of the fill-volume shelf-life specification to reflect [ ], since the target fill volume of the drug product [ ] Resubmit the revised drug product specification that reflects the above changes. (comment 11.b.)

d. The foreign particulate matter data on [ ] lots, submitted earlier [ ] pp. 149-175, v 1.6, March 27, 1998, submission) indicate a *mean* range of 121- 682 particles > 1.1 µ in size. In your amendment dated December 03, 1999, you report values [ ] without any additional information. Explain and rectify the discrepancy observed between these two sets of data. Furthermore, identify the types of particles [ ] investigate the source(s) of these particles, and institute corrective measures to control their presence to an acceptable level in the drug product through its shelf-life. Resubmit a revised drug product specification that reflects the above changes. (comment 11.c.)

e. Retain the format of drug product release and shelf-life specification documents as provided in May 19, 2000, amendment. Revise the proposed drug product specifications to reflect the above changes in comments 2.a. through 2.d., and resubmit updated drug product specifications using the same format as in the May 19 amendment. (comment 11.a.(1))

f. Provide a system suitability chromatogram showing adequate resolution of [ ] from other impurities/degradation products of albuterol in the drug product as an integral part of method [ ] Revise and resubmit the updated method. (comment 12.d.)

3. The following comments pertain to [ ] thereof.

a. Revise method — , for IR identification specification, to state "matches to that of USP reference standard for polyethylene" (Vol. 5, p. 0046). Additionally, include representative IR scans of all reference standards that are used in this test [ ]. (comment 13.b.)

b. The following comments pertain to [ ]

(1) Based on the differences observed in [ ] and [ ] demonstrate with appropriate analytical procedure(s) conditions (sa[ ]

[ ] (comment 13.c.)

(2) The acceptance criteria ([ ] proposed to assure batch-to-batch consistency of the [ ] are non-discriminatory and inadequate ([ ] , p. 0253/Vol. 5). As indicated in comment 3.b.(1) above, identify the [ ] profile both in [ ] Based on these profiles, propose an adequate specification for [ ] in a suitable solvent, with supportive data. (comment 13.d.)

(3) The proposed HPLC Method [ ] does not provide needed procedure to monitor unusual impurities in the [ ] of the [ ] Provide the limit of detection and limit of quantitation of method for [ ] To allow evaluation of the method, provide appropriate chromatograms for the reference standard of aqueous [ ] and suitable worksheet(s) to record the results. Additionally, clarify the course of action to be taken if "unusual peaks" are observed. (comment 13.d.)

(4) Based on the data submitted in response to comments 3.b.(1)-(3) above, if a [ ] approach is deemed appropriate, the proposed limit for [ ], determined [ ] by method [ ] is not supported by the data provided on [ ] lots of the [ ]. Tighten significantly the proposed specification for [ ]. (comment 13.d.)

c. The proposed specification of [ ] is not acceptable when the level of [ ] in a vial is estimated to be less than [ ] In collaboration with the DMF holder, [ ] (DMF [ ] revise the specification for [ ] and support the specification with adequate data (e.g., lot analysis). Additionally, advise [ ] to acknowledge their commitment to report the amount of [ ] found on the certificate of analysis (COA)

accompanying each lot, as an amendment to their DMF [ ] See related comment 13. (comments 13.d. and 13.e.)

d. The proposal to test [ ] lot of the [ ] per year for [ ] as routine testing is not sufficient to provide batch-to-batch quality assurance and is not acceptable. Once a sufficient database is established to assure batch-to-batch consistency of the [ ] a reduced number of lots, depending upon the number of lots procured in a year, may be considered for routine testing. (comment 13.d.)

e. Resubmit the updated acceptance specifications for the [ ] that reflect the changes in comments 3.a. through 3.d. above.

4. The following comments pertain to the proposed AccuNeb paper label (including its components: [ ]. If [ ] vials are [ ] instead of using paper labels, comments 4-7 need not be addressed. (comment 14)

a. Revise the specifications for the paper label to reflect comments 4.b. through 4.d. below, and resubmit the updated specifications.

b. The proposed acceptance specifications for [ ] of the paper label are not acceptable. The chromatographic data [ ] provided in this regard are inadequate and inconclusive (Vol. 6, pp. 0044, 0045, and 0048). To ensure consistent quality of [ ] paper label components [ ] and the paper label itself, address the following comments. (comment 14.a.)

(1) Demonstrate with appropriate data that [ ]

In addition, propose acceptance criteria for [ ] the paper label, supported by adequate data. (comment 14.a.)

(2) Additionally, in collaboration with the manufacturers of the

[

] Revise method [ ] accordingly and resubmit the updated method. (comment 14.a.)

c. Explain the procedure for sample preparation for the identity of [ ] the paper label, by IR and as part of method [ ] Provide an IR spectrum for [ ] reference standard. Revise and resubmit the updated method. (comment 14.a.)

d. Provide the chemical names/components for [ ] and all the [ ] dyes that are used in the manufacture of the paper label stock. (comment 14.b.)

5. The following comments pertain to [ ] the paper label. (comment 14.c.)

a. The holder of DMF [ ] has not responded adequately to our letter dated January 25, 1999, and as a result, the DMF remains inadequate to support your application. A letter has been issued to [ ] the holder of DMF [ ] comment 14.c. and 14.d.)

b. Address the following comments pertaining to [ ] collaboration with [ ] the holder of DMF [ ] (comment 14.c.)

(1) Clarify and rectify the discrepancies noted with the chemical components of [ ] Contrary to the DMF holder's claim that [ ] complies to FDA regulation [

]

Redacted 4

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

c. Additionally, in collaboration with the manufacturers of the components of

d. DMF for the proposed has been found to be inadequate in its support of your application. The holder of DMF has been issued a letter. (comment 17)

10. The following comments pertain to the stability protocol.

a. As requested earlier, monitor foreign particulates through the shelf-life of the drug product and provide data. (comment 19.b.)

b. The proposal to place of the lots produced per year (or a minimum of lot) on annual stability testing after the marketed production batches is not adequate to assure batch-to-batch quality of the drug product. As requested earlier, revise this number to be proportional to the production rate of the drug product. (comment 19.c.)

c. Comments on the frequency of testing through the shelf-life of the drug product are deferred at this time, until the issues raised in comments 4 - 9 of this letter are satisfactorily resolved. (comment 19.b.)

11. The following comments pertain to the proposed stability specifications and the stability data submitted for the drug product.

a. You are reminded of your commitment to reevaluate and revise the (NMT if needed, when data from at least additional lots of the drug product are available. (comment 20.a.)

b. Provide the outcome of your investigation into the significant variation observed with the levels of degradation product [ ] in stability data for Lots F513, F512, E006B-E071B. (comment 20.b.).

c. Provide updated stability data for the [ ] lots of the drug product ( ) that have been packaged in [ ]. Also, pool the formal stability data for these [ ] lots by attributes of the drug product at each storage condition, as requested earlier (comment 20.i.). Submit both a paper copy and an electronic copy (e.g., Excel, Word, etc.) of the pooled stability data. Comments pertaining to the proposed expiration dating of [ ] are deferred at this time. (comments 20.h. - 20.i.)

12. Concerning the [ ], we reiterate our request for a 90 day inhalation toxicology study to qualify the [ ]. This study should be conducted expeditiously, however, the results of this study may be submitted as a Phase 4 commitment, within 12 months of approval if not available beforehand. Your response that the impurity is present at similar levels in marketed Ventolin products is insufficient, because drug approval criteria have evolved since the time that Ventolin was approved, and current standards are being applied to your application. Because individual impurities were not as tightly controlled at the time Ventolin was approved, we do not know whether the [ ] has always been present in Ventolin or if it appeared later as a result of a manufacturing or other change. Thus, the extent to which the marketing safety database applies to your product is undefined. (comment 23)

13. In reference to your response to comment 3.c. above, you must qualify your specification for [ ]. If sufficient information is not available in the literature, conduct a 90-day inhalation toxicity study in an appropriate animal species. The study should include a histopathological evaluation of a complete battery of tissues.

Note that information submitted to this NDA that does not pertain to AccuNeb Inhalation Solution is not considered to be part of this NDA and will not be reviewed. Refer to comments 12.c., 12.d., and 12.g. in our March 30, 1999, letter to this NDA. We also refer to a July 23, 1999, teleconference between representatives of Dey L.P. and FDA, for our request that sections of the NDA not pertaining to AccuNeb Inhalation Solution be removed.

In addition, it will be necessary for you to submit draft labeling in response to the suggested preliminary revisions 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

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

cc:
Archival NDA 20-949
HFD-570/Div. Files
HFD-570/Hilfiker
HFD-570/Whitehurst
HFD-570/Huff/6-1-00
HFD-570/Uppoor
HFD-570/Wilson/6-2-00
HFD-570/Anthracite/6-2-00
HFD-570/Chowdhury/6-2-00
HFD-570/Shah/6-2-00
HFD-570/Poochikian/6-2-00
HFD-570/Himmel/6-5-00
HFD-570/Meyer/6-2-00
HFD-002/ORM
HFD-102/ADRA
HFD-40/DDMAC (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

/S/ 6/6/00
/S/ 6/6/00
/S/ 6/6/00
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/S/ 6/6/00
/S/ 6/6/00
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Drafted by: HFD-570/Hilfiker/May 31, 2000
Initialed by: HFD-570/Barnes/6-1-00
HFD-570/Choi (for Uppoor)/6-2-00
Final: HFD-570/Hilfiker/6-2-00
Filename: c:\my documents\N 000531aeltr

APPROVABLE (AE)

NDA 20-949 MAR 30 1999

Dey Laboratories
2751 Napa Valley Corporate Drive
Napa, CA 94558

Attention: Peggy J. Berry
Regulatory Affairs Project Manager

Dear Ms. Berry:

Please refer to your new drug application (NDA) dated March 27, 1998, received March 30, 1998, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for albuterol sulfate inhalation solution,

We acknowledge receipt of your submissions dated May 18, June 9, 15, and 19, July 1 and 17, September 15 and 29, and October 6, 1998.

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

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

   a. Several comments pertaining to the drug substance, albuterol sulfate, have been forwarded in a letter dated February 26, 1999, [ ] the holder of DMF [ ]

   b. Clarify the statement "albuterol sulfate reference standards are qualified according to the USP" (p. 252/vol. 1.2). Indicate the source of the albuterol sulfate reference standard and provide information on any [ ] steps (if performed). Additionally, establish and submit tighter acceptance specifications for the drug substance reference standard than the acceptance specifications of the drug substance to assure consistent quality of the incoming albuterol sulfate.

2. The following comments pertain to the albuterol sulfate drug substance specifications.

   a. Any impurity/degradation product observed at [ ] in the drug substance needs to be identified, individually controlled, and qualified. All identified impurities at their proposed specification levels need to be qualified. Alternatively, you may revise the specification to [ ] w/w for

impurities [ ] and (see comment 2c). For qualification of impurities [ ] refer to comment 23.

b. Revise the specification proposed for the impurity/degradant, [ ] [ ] [ ], to "Not more than [ ] due to its mutagenic potential.

c. As indicated below, revise the specifications proposed for all identified impurities [ ] and total impurities to reflect the actual data observed for the manufactured lots of albuterol sulfate (e.g., release data, stability data, and the certificate of analysis: vol. 1.2, pp. 32, 37; vol. 1.4, p. 177). Additionally, establish an adequate specification with appropriate supportive data for total unspecified impurities/degradation products.

[

]

d. Provide an appropriate quantitative color test ([ ]) complementing the physical appearance to detect any subtle color changes that may occur in the drug substance which could go unnoticed by mere visual observation.

e. In consultation with the holder of DMF [ ] establish adequate specifications for the [ ] that are used in the synthesis/manufacture of the drug substance, rather than proposing the specifications for the [ ] solvents that are mentioned under USP <467> but have not been used in the manufacture of the drug substance. Support these specifications with appropriate data.

Similarly, if any have been used in the manufacture of albuterol sulfate, establish adequate specifications with appropriate supportive data for the residual metals carried over The proposed drug substance specifications should be inclusive of all of the test

attributes listed in DMF [ ] for the drug substance, albuterol sulfate (see comment 1a).

f. For batch to batch consistency of the drug substance, replace the [ ] with the pH specification of an x % solution of the drug substance. The [ ] test may be retained as an in-process control test.

3. The following comments pertain to the test methods used for the drug substance, albuterol sulfate.

a. As a part of identification methods [ ]' (vol. 1.2, p. 197) and [ ] (vol. 1.2, p. 217) for albuterol sulfate, include [ ] of both the reference standard and the sample used in the relevant methods as appropriate and resubmit the methods.

b. As a part of method [ ] for the detection of [ ] in albuterol sulfate, include typical gas chromatograms that are representative of the sample and standard preparation (vol. 1.2, p. 274). Additionally, the information provided in the method (vol. 1.2, pp. 274, 276, and 278) for the detection of [ ] in [ ], is not relevant to this NDA and should be deleted. Resubmit the updated method.

4. The following comments pertain to the validation data for method [ ] for the assay of impurities/degradation products in the drug substance, albuterol sulfate. As appropriate, these comments are equally applicable to method [ ] used for the drug product.

a. Establish the [ ] as integral parts of the system suitability test (for acceptance, release, stability, and impurities/degradation methods) for test method Establish a [ ] see comment 4b).

b. Include all [ ] impurities/degradation products (as listed on p. 22/vol. 1.2) at their detection levels in the standard preparation for impurities. As a part of the system suitability parameter, use these impurity standards to establish/define a resolution factor. [ ] should be sufficient to ensure adequate resolution and thereby accurate quantitation of albuterol and its impurities/degradation products. The following are examples of closely

[ ] need better resolution: resolution of the degradation product [ ] from albuterol (Figure 4, p. 34/vol. 1.4); and incomplete resolution of impurity [ ]) (p. 56, vol. 1.4) and from the [ ] impurity [ ]). Provide representative chromatograms to demonstrate the resolution of albuterol and its impurities/degradation products from each other.

c. Provide a limit of detection and a limit of quantitation for identified impurities [ ] Additionally, provide relative response factors for all identified impurities/degradation products. If the relative response factor is not the same as the parent molecule, albuterol, include a correction factor specific to each individual impurity/degradation product in the method for its accurate quantitation.

d. Provide appropriate confirmative data to ensure that the peak appearing at [ ] (Figures 5, 6, and 8-9, pp. 35-39, vol. 1.4) is truly an artifact of [ ] rather than [ ], over a period of time.

e. Indicate/specify the type of chromatographic equipment and the columns used in the ruggedness study of method [ ] 5 performed by [ ]

f. Increase the [ ] of albuterol so that it is greater than [ ] to ensure adequate separation of all — impurities.

g. Use a uniform notation, either arabic numerals [ ] or alphabetic letters [ ], for labeling of the identified impurities to avoid confusion (see pp. 27 and 29/vol 1.2, versus pp. 21, 30, and 55/vol. 1.4).

h. Consolidate all of the chromatographic data that are presented in more than one chemical report for the identified impurities/degradation products of albuterol into one method validation report to demonstrate the selectivity/specificity of method [ ]

5. The following comments pertain to validation data provided for method [ ] for the determination [ ] in the albuterol sulfate drug substance.

a. In order to ensure accurate quantitation of [ ] in the drug substance, establish the [ ] for [ ] as a part of the system suitability parameters. [ ] is not adequate as demonstrated in the chromatogram in Figure 1 (p. 77/vol. 1.4). Establish a [ ] Alternatively, provide appropriate data to substantiate the claim that the [ ] does not interfere in the quantitation of [ ]

b. Provide the [ ] observed in the drug substance. Clarify whether this [ ] corresponds to any of the impurities analyzed by method [ ]

c. Explain the variability in % RSD (5.1 vs. 11.6) observed for the [ ] in Table 1 (p. 75, vol. 1.4) in the albuterol sulfate solution (5 mg/mL) containing [ ]. Use a [ ] validation of the precision of the method.

d. Resubmit appropriate chromatograms with legible units of measurement on each axis. An expanded/truncated region of a chromatogram should be complemented with a complete run time chromatogram.

e. In addition to the validation data submitted in the NDA, provide accuracy, precision and linearity data for method [ ] Provide the relative response factor and the limit of quantitation for [ ] For guidance on the validation of HPLC methods, refer to the FDA/CDER publication, "Validation of Chromatographic Methods," dated November 1994.

6. The following comments pertain to the degradation studies of the drug substance.

a. Conduct the photostability testing for the albuterol sulfate drug substance as per the ICH guidelines/conditions as a minimum. The photostability testing conducted [ ] is not adequate for confirmatory studies. This comment is equally applicable to albuterol sulfate inhalation solution.

b. The degradation [ ] observed due to [ ] of albuterol sulfate do not appear to be adequately resolved from the albuterol sulfate [ ] (Figure 1, p. 132/vol. 1.4), as you have claimed. Provide appropriate data to

support the claim. Otherwise, establish [ ] as a system suitability parameter between the [ ] in the chromatogram. Refer to comments 4a-b above regarding method [ ].

c. Clarify the difference between [ ] solutions prepared for the forced degradation studies of albuterol sulfate (p. 129, vol. 1.4). Clarify the nature [ ] observed in Figure 4 for the [ ] (vol. 1.4, p. 132). Resubmit all of the chromatograms [ ] for further evaluation.

d. Clarify what [ ] of albuterol sulfate (p. 32/vol. 1.2). Clarify whether the limit of detection is the same for all of these impurities (see comment 4c above).

7. Since the sterility of the finished dosage form [ ] also depends on the microbiological quality (bio-burden) of the drug substance, establish appropriate test method(s) and microbial limits with supportive data for the drug substance (albuterol sulfate) in order to assure the quality, purity, and strength of the finished drug product (albuterol sulfate inhalation solution).

8. With reference to the polyethylene bags (the immediate container closure for the packaging of the albuterol sulfate drug substance), cite specific supportive appropriate indirect food additive regulation(s) governing their suitability as a basic component in direct contact with foods. Alternatively, provide this information through the holder of the drug substance DMF.

9. Revise the stability protocol for the drug substance, albuterol sulfate, to include the test attributes, and resubmit the revised stability protocol with the available updated stability data (vol. 1.2, p. 36-37).

10. The following comments pertain to the executed batch records for albuterol inhalation solution.

a. Explain why [ ] has been used in the manufacture of batch E622 of the drug product, even though it is not a component of the drug product formulation ([ ] pp. 291-292/Vol. 1.4).

b. With reference to this NDA, explain the relevance of the documents in [ ] language which are attached to the master batch records for Lot

E067A (vol. 1.5, pp. 80, 87, 94, 101, 155, 162, 169, and 172). The chemical structure depicted in each of these documents do not correspond to albuterol sulfate. Resubmit all updated documentation.

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

a. The following comments pertain to impurities/degradation products in the drug product.

(1) In the drug product specifications, list all of the impurities that are controlled at the drug substance level and do not increase upon storage, with a footnote stating these impurities are controlled at the drug substance level.

(2) Identify any degradant at or above [ ] in the drug product.

(3) Tighten the specifications to reflect the actual observed data (as indicated below) for the following impurities/degradation products:

[

]

No.	Impurities/Degradation products	Release Specs.	Stability Specs.

Furthermore, since the degradation product, [ ] has now been identified as [ ], replace it with its new name and list it as a degradation product. Resubmit the revised drug product specification document to reflect this change. (Refer to comments 20b through 20f.)

b. Establish appropriate test methods and specifications (release and stability) supported with adequate data for the fill volume/delivered volume/fill weight throughout the shelf life of the drug product.

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	
NMT	
NMT	

d. Revise the proposed specification for content uniformity for further clarification as indicated below. The sample specification given below for the 0.042% w/v strength of albuterol sulfate inhalation solution is also applicable to the 0.021% w/v strength. Additionally, provide raw content uniformity data collected for each individual vial.

Content Uniformity
0.042 % Solution:

If one vial is outside the [ ] range but not outside the [ ] range, or if the standard deviation is greater than [ ] but NMT [ ] or if both conditions prevail, [ ] vials.

e. Indicate the units of measurements for the proposed specifications of in the drug product/drug substance specification document(s). Express units of measurement in % weight/weight rather than % area/area, whenever possible.

f. Use a more specific identification test (e.g., IR) for albuterol in the drug product, in addition to the proposed [ ]

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

a. With reference to [ ] (vol. 1.2, pp. 64 and 302), provide the levels and frequency at which they are found/observed. Additionally, clarify whether [ ] impurities/degradation products.

b. With reference to methods for [ ] determination of the drug product, respectively, include a test result worksheet for release testing similar to in-process and stability samples.

c. The test method (vol. 1.2, p. 232) for odor, color, clarity, and appearance, 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 [ ] 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 (vol. 1.3, pp. 132-135).

f. The test method, , for foil pouch [ ] could not be found within the submission. Provide the method for evaluation. Additionally, clarify whether test method is a part of overwrap [ ] test (vol. 1.3, p. 118).

g. The test method for content uniformity of an inhalation solution in a unit-dose container, should indicate that it follows compendial procedure as per current USP <905>. Any references or information provided for the drug products other than albuterol sulfate inhalation solution [ ]
[ ]

[ ] are not relevant to this NDA and should be withdrawn from this method (vol. 1.3, pp. 93-96). Resubmit a revised method accordingly.

13. The following comments pertain to a component of the LDPE vial, [ ]

a. A letter dated January 25, 1999, has been issued to the holder of DMF [ ] for their product, [ ]

b. With reference to the IR identification specification statement for and to the statement "matches that of standard," clarify what is meant by "standard" and identify the source of this standard (vol. 1.2/p. 48).

c. Using appropriate analytical method(s), establish an [ ] profile of [ ] and include it as an acceptance specification to ensure batch-to-batch consistency of incoming [ ] material. Provide sample preparation and [ ] conditions for [ ] if it differs from USP <661>.

d. The proposed specifications for [ ] are not reflective of the results obtained (vol. 1.6/p. 056) and are not acceptable. Establish adequate limits supported with data [ ] [ ] If the level [ ] is very low, a limit on the total weight of [ ] may be established. Provide actual data for the quantity (µg) of [ ] Revise the proposed specifications for [ ] to reflect the actual data obtained from [ ] (vol. 1.2/p. 48; vol. 1.6/p. 056).

e. Confirm with appropriate data that [ ] LDPE vial (53133-014) is truly due to an [ ] (vol. 1.6, pp. 97 and 134). Additionally, confirm that no [ ] LDPE vials during the [ ] operation.

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 [ ] in [ ] 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 [ ] 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 [ ] to ensure consistent quality [ ] 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 [ ]. Alternatively, [ ] may submit this information to the Agency in a type III DMF to ensure consistent quality of the [ ]

g. Provide the quantitative chemical composition for each of the [ ] that are used in various types of inks (e.g., [ ] (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 [ ]. Alternatively, [ ] Inks may submit the above information to the Agency in a type III DMF to ensure consistent quality of inks for the paper labels.

15. The following comments pertain to foil-[ ] pouch. [ ]

a. The holder of DMF [ ] has been issued a letter dated January 25, 1999, for the foil- [ ]

b. Provide the quantitative chemical composition for the following components of the foil-[ ]

references to indirect food additive regulation(s) under which the indicated/identified constituent(s) of each foil-[ ] component is considered suitable for their intended use. Alternatively, provide this information via appropriate authorized DMF reference(s).

c. To ensure consistent batch-to-batch quality of incoming foil- [ ] [ ], establish an extractable profile for [ ] in appropriate [ ] solvents. Establish adequate limits supported with data for [ ] If the level [ ] is very low, a limit on the total weight [ ] may be established. Revise and resubmit the acceptance specifications, , for foil-[ ] reflect the above comments.

16. Revise the leachables study of the packaging components (vol. 1.6/p. 177) to provide the following information.

    a. Include a representative chromatogram of a composite sample prepared from all extracts . Characterize/identify each individual packaging component by appropriate sensitive analytical techniques [ ] Additionally, provide a limit of detection and a limit of quantitation of the [ ] method used for this study.

    b. Include representative sample chromatograms of the stability samples and the chromatographic parameters used in their analysis.

    c. Submit appropriate conclusive data [ ] to demonstrate the absence of any leachables in the drug product from the packaging components.

17. In the discussion during a teleconference dated August 17, 1998, you indicated your intent to replace overwrap foil-[ ] with a new overwrap to eliminate the [ ] into the drug product arising from the [ ] [ ]. You also indicated that you would provide supportive information pertinent to this new overwrap (e.g., quantitative composition of all the components, appropriate references to indirect food additives regulations, acceptance specifications, authorized DMF references, leachables study, and appropriate drug product stability data). We remind you of your commitment to provide pertinent supportive information for the new foil-[ ] Comment 16, pertaining to leachables, is equally applicable to the new overwrap.

18. The following comments pertain to the [ ] of albuterol sulfate inhalation solution (appendix 6/vol. 1.5, pp. 211-280).

    a. The manufacturing [ ] is not clear.

    [

    ]

    Provide a statement to define the machines intended for this product and a summary of the most recent fill(s) on the appropriate machines.

    b. The methods and limits for bioburden in the bulk drug solution were not provided. Provide the referenced [ ]or describe the

appropriate microbiological methods. Provide acceptance specifications for bioburden in the compounded bulk solution.

c. Bioburden data provided on page 277 (vol. 5) for '
' were described as "typical," but do not state whether the samples were collected from either product formulation. Describe the source of these counts.

d. Summarize your validation of the [ ] studies, including methods and data. These may be provided by reference to another product of the same or similar composition, or if new studies are needed, by a commitment to provide these data within 6 months following approval.

e. Provide fill dates for the media fill data and indicate whether these fills are successive. If interceding fills were performed, particularly failures, these should be included and noted. Provide a discussion of any failed media fills.

f. USP has amended its sterility test parameters to increase the incubation time to 14 days for all samples including those processed by membrane filtration (see USP 23-NF, Eighth Supplement, May 15, 1998, pp. 4295-4299). Adjust your method accordingly.

19. The following comments pertain to the post-approval stability protocol.

a. In addition to the long term storage conditions, include accelerated and intermediate storage conditions with an appropriate test frequency, with a footnote indicating that the drug product may need to be placed on intermediate storage conditions if significant change is observed at accelerated storage conditions.

b. In order to ensure consistent quality, purity, and strength of the drug product, include per container as attributes in the stability protocol and monitored throughout the shelf life of the drug product.

c. The number of batches to be placed on stability annually after the marketed production batches should be proportional to the production rate of the drug product (i.e., number of lots/year) instead of one batch/year.

20. The following comments pertain to the stability specifications and stability data of the drug product.

a. Revise the proposed stability specification, NMT [ ] for the color of the solution to reflect the actual observed data [ ]

b. Clarify what the two values presented for each impurity/degradant at every time point represent in the submitted stability data for Lots F513, F512, E066B-E071B. Clarify whether they represent results of [ ] same sample or [ ] Additionally, explain the significant difference observed in the two values [ ] (vol. 1.2, pp. 76, 80, 82, 84, 85, 90, 92, 94, 95, 97, 98, 100, and 102).

c. The proposed release and shelf life specifications for [ ] and [ ] respectively, for the drug product are not justified based on the submitted stability data (vol. 1.2, pp. 71-106) and should be tightened accordingly. Otherwise, note that a degradant at the proposed limit should be qualified [see comments 11a(2) and 11a(3)]. Additionally, express the specification and the data as % w/w rather than % a/a.

d. Based on the presented stability data, explain the [ ] (Refer to vol. 1.2, pp. 76-102). Additionally, express the data in units of % w/w rather than % a/a. Reevaluate and support the proposed specifications [ ] either at release or throughout the shelf life of the drug product based on the available data [see comments 2c and 11a(3)].

e. Explain the [ ] especially at the accelerated storage conditions in the drug product. (Refer to vol. 1.2, pp. 81-102). In light of this observation, reevaluate the release/shelf life specifications of [ ] in the drug substance or in the drug product to reflect the actual data [see comments 2c and 11a(3)].

f. Initiate appropriate controls and measures to limit the formation of [ ] in the drug product, due to its mutagenic potential. The proposed release and shelf life specifications for [ ] respectively, are not justified and should be tightened, preferably to [ ] [see comments 2c and 11a(3)].

g. Revise method [ ] to obtain baseline [ ]

h. Submit updated stability data for lots E622, E623, F512, F513 and lots E066B-E071B to support the proposed specifications and the expiration dating of — from the date of manufacture of the drug product.

i. In addition to the existing format of reporting stability data, pool the formal stability data for all the NDA batches, if possible by attributes (e.g., assay, color, pH, delivered weight/volume, particulate matter, impurities/degradation products etc.), for each storage condition. Submit both a paper copy and an electronic copy (e.g., Excel, Word, WordPerfect etc.). For example:

Impurities/Degradation products: Total Impurities											
		0.021% w/v					0.042% w/v				
Stability Condition	Months	E622 250 L	F513 300 L	E06B 500 L	E069B 500 L	E070B 500 L	E623 250 L	F512 300 L	E06B 500 L	E06B 500 L	E07B 500 L
		% w/w	% w/w	%w/w	% w/w	% w/w	% w/w	%w/w	%w/w	%w/w	%w/w
28°C	0										
	3										
	6										
	9										
	12										
	18										
	24										
	Expiry (E)										
40°C	0 to 6										
25°C/ 35%RH	0 to E										
40°C/ 15% RH	0 to 6										

21. Submit the method validation package in triplicate as per 21 CFR 314.50(e)(2)(i) and 21 CFR 601.2, which includes all of the updated information requested above for test methods for the drug substance and the drug product.

22. As per the National Environmental Policy Act, Revision of Policies and Procedures, which went into effect August 28, 1997, you are not required to submit an environmental assessment if you can meet the conditions set in 21 CFR § 25.15(d). You may withdraw the environmental assessment report and resubmit the claim for a categorical exclusion from the environmental assessment with the appropriate CFR citation under which the waiver/withdrawal of environmental assessment is qualified [e.g., 21 CFR 25.30, 21 CFR 25.31(a), 21 CFR 25.31(b), or 21 CFR 25.31(c)].

Additionally, provide a statement that "To the applicant's knowledge, no extraordinary circumstances exist."

23. You have requested specifications [ ] 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 [ ] 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 these [ ] to [ ]

24. If it remains your intention to utilize the foil overwrap from which [ ] leached into the drug solution, you will need to qualify [ ]. If there are insufficient data available in the literature, perform a 90-day inhalation study to qualify [ ] This study should include histopathological evaluation of a complete battery of tissues. In addition, because the [ ] suggests that it may react with DNA, you must evaluate its genotoxicity. A minimum evaluation may include an Ames test and a mouse lymphoma TK assay.

25. In a September 29, 1998, correspondence regarding DL-009, you stated that "when the ITT population (referred to as 'evaluable') was defined in accordance with the Investigator's final report, that population data did not match the report." You stated that the data diskette and the data used by — for the integrated analysis were compared and were identical. Therefore, the available population definitions from DL-019 were used for analysis. The data were sent with 2 fewer patients in each of the 0.75 mg and placebo groups. You further stated that the %ΔAUC FEV1 variable in the September 29 correspondence was consistent with the analysis of DL-019. Provide an explanation of why these 4 subjects were eliminated, and what is meant by the above statements.

26. There is a discrepancy between change in heart rate data from DL-009 (vol. 1-12, p. 99) and the data in Table 8.3.1 in Appendix B (vol. 1-38). Clarify if these discrepancies are solely due to the fact that the former includes 28 patients and the latter includes 29 patients.

27. Submit the case report form of the study subject (DL-019, Table 35, vol. 1-16) in the 1.5 mg group with a new instance of a depressed ST segment observed at Visit 2, 30 minutes post-dose. This depressed ST segment was not mentioned pre-dose and was still present at 60 and 90 minutes post-dose. Additionally, provide any details on this observation in this subject.

28. In Study DL-019, the 0.75 mg dose often had higher values than the 1.5 mg dose after the first dose of the drug at Visit 2. Verify that the 0.75 mg and 1.5 mg doses were not mislabeled and mistakenly switched at Visit 2 but were correctly labeled at Visit 4 or were not switched in the analysis.

29. According to the Integrated Clinical and Statistical Report narrative, Patient No. 157 had results interpreted by the centralized cardiologist as clinically relevant that were considered irrelevant by the investigator. Clarify what findings on the EKGs of Patient No. 157 were considered to be relevant.

30. In Data Listing 14 (vol. 1-26, data on DL-019 EKGs), there is a classification called "deteriorated (from baseline)." Clarify the meaning of this term.

31. With reference to the Integrated Clinical and Statistical Report for DL-019, Table M ("Summary of Adverse Events that occurred in > 2% of the ITT Population") and Table N ("Summary of Potentially Drug-Related Adverse Events") do not explain the difference between worsening of asthma symptoms versus an asthma exacerbation. Provide an explanation of how this distinction was made. More exact terms should be provided for these groupings.

32. For future study report submissions, also provide a more conventional method (e.g., ANOVA) for analyzing study data if a Nonlinear Mixed Effects Model (NONMEM) analysis is used.

The following preliminary labeling comments are provided. Additional comments will be forwarded following review of the response to this letter.

33. The proposed tradename, ——— is not acceptable. Provide an alternative proposed tradename in writing.

34. Revise the tradename to describe the product in terms of dose instead of concentration. For example, the tradename should be expressed as albuterol sulfate inhalation solution, 0.75 mg, instead of albuterol sulfate inhalation solution, 0.021%. This comment applies equally to the 0.042% strength.

35. Include in the package insert the graphs from Study DL-019 regarding the % change in FEV_1 from pre-dose versus time at Visits 2 and 4 for both doses of albuterol sulfate and placebo. Include a horizontal line depicting the 15% level on the graph so that one can see where the curve crosses the line.

36. Albuterol sulfate inhalation solutions, 0.021% and 0.042%, are indicated for use in

patients 2-12 years of age. Clarify this age range in the package insert and all carton and container labeling to avoid misintended use of these products in adults. Specify appropriate age groups in the INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections of the package insert.

37. In the draft package insert, reference [ ] " actually refers to rescue medication use. Therefore, this reference appears to be wrong. Provide the correct reference.

38. Albuterol sulfate inhalation solutions, 0.021% and 0.042%, are indicated for use in subjects 2-12 years of age. Efficacy data referring to subjects greater than 12 years of age should not be included in the package insert.

39. Revise the CLINICAL PHARMACOLOGY, Pharmacokinetics subsection of the package insert according to the most recently approved package insert for Ventolin™ (albuterol sulfate) Inhalation Solution. In addition, add the following sentence to the end of this subsection: '[ ]

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 314.120. 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,

/S/

John K. Jenkins, M.D., F.C.C.P.
Director
Division of Pulmonary 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/Schumaker/3-19-99
HFD-570/Jenkins/3-28-99
HFD-570/Whitehurst/3-29-99
HFD-570/Huff/3-26-99
HFD-570/O'Hearn/3-24-99
HFD-570/Himmel/3-23-99
HFD-570/Shah/3-29-99
HFD-570/Schroeder (for Poochikian)/3-29-99
HFD-570/Aras/3-26-99
HFD-570/Wilson/3-26-99
HFD-570/Chen/3-24-99
HFD-570/Uppoor/3-25-99
HFD-002/ORM
HFD-102/ADRA
HFD-95/DDMS
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: HFD-570/Hilfiker/March 10, 1999
Final: HFD-570/Hilfiker/3-29-99
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APPROVABLE (AE)

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