

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20950

ADMINISTRATIVE DOCUMENTS

Division Director's Memorandum

Date: Thursday, May 27, 1999
NDA: 20-950
Sponsor: Dey Laboratories
Proprietary Name: Duoneb (albuterol sulfate 3.0 mg / ipratropium bromide 0.5 mg)
Inhalation Solution

Introduction: This is an NDA for an inhalation solution for nebulization that combines ipratropium and albuterol in a single drug product. This combination has previously been approved as the Combivent Inhalation Aerosol, developed and marketed by another sponsor. This application is a 505(b)(2) application, referencing the albuterol inhalation solution and ipratropium inhalation solution products, but not the Combivent Inhalation Aerosol, which is still under exclusivity (*see conclusions*). Therefore, the sponsor had to support the safety and effectiveness of the combination of these two drug substances, including meeting the combination policy.

CMC: Like many of Dey's products, these LDPE vials as proposed utilize a paper label. Unlike some of Dey's generic products, this product is proposed to have an overwrap to protect the product from egress of moisture and ingress of undesirable volatile substances. Several CMC issues will need to be addressed by the sponsor prior to approval of this product, as detailed in Dr. Kim's review. Many of these are shared with NDA 20-949, the recently reviewed NDA from Dey for lower dosage albuterol sulfate inhalation solutions. Interestingly, one issue in this NDA is that a volatile impurity is released by the overwrapping itself and enters into the drug solution -¹

A microbiology consult was sent, since such inhalation drug products should be sterile. The consult found the application satisfactory and the relevant comments related to remaining microbiologic concerns were included in the action letter as part of the CMC comments.

Pharmacology/toxicology: The main pharmacology/toxicology issue for this NDA were that the FDA could not refer to the Combivent findings to assume the safety of this combination, due to exclusivity. The sponsor therefore had to submit studies looking at whether ipratropium potentiated the toxicologic effects of albuterol. A further issue is the safety of the impurity¹ which ties in with the CMC review. This latter issue remains the sole pharm/tox issue to be resolved prior to approval (except for labeling).

Biopharmaceutics: The sponsor submitted one biopharmaceutics study, in accordance with prior discussions with the Division. This study essentially examined whether the presence of ipratropium altered the pharmacokinetics of albuterol. Due to the poor absorption of ipratropium by the inhaled route, its own pharmacokinetics were not explicitly explored in this trial. Apart from labeling, all biopharmaceutic issues for approval have been resolved.

Clinical / Stastical: Under agreement with the Division, the clinical program for this application was focused on showing the combination product to be superior to its

components administered singly. This was done via a large multi-period cross-over / parallel group study (and literature submissions). The clinical review was performed by Dr. Anthracite with secondary reviewing by then Division Director – Dr. Jenkins. The data from the sole study – DL-024 indeed showed that the Duoneb product provided faster onset, greater FEV₁ response and somewhat longer duration of action than either single component. One issue for this product is the presence of EDTA in the solution (for stability purposes). EDTA, though not potently so, can lead to bronchospasm. Duoneb contains 0.1 g/L, a concentration lower than that reported to be capable of inducing bronchospasm in the literature (> 1.2 g/L). Since the ipratropium single product comparator contained no excipients, the spirometry results from DL-024 allowed for an examination of paradoxical bronchospasm due to Duoneb. No indication of such events were seen (in fact, Duoneb had fewer such significant events than ipratropium). The drug appears to be sufficiently safe and effective for approval and there are no clinical issues that would preclude approval at this point.

No pediatric data are a part of this NDA and, given the indication for COPD, this is appropriate.

Auditing / Data Checking: The Division elected not to request routine DSI audits of this study due to the known efficacy of these agents and the combination. No circumstances that would have elicited a “for cause” audit were discovered in the review. The medical officer performed his own auditing of the data versus study reports without any significant problems being identified.

An EER was sent leading to an inspection of the relevant facilities (the drug substance manufacturers in Italy and the drug product production site in Napa, CA) in September and October of 1998. All sites were found acceptable.

Labeling: The labeling as submitted is somewhat spare, and will need to be augmented. Many of the review disciplines have preliminary labeling comments that should be forwarded to the sponsor. However, since this review will not lead to an approval, final labeling will not be arrived at for this review cycle.

Conclusions: This NDA will be given an approvable action, since there are significant remaining CMC issues that preclude approval at this time. Apart from these issues, the application is acceptable, though final labeling will not be arrived at with the sponsor until such time that the CMC issues are resolved. Finally, it should be noted that a full approval would likely not be possible now, due to pertinent exclusivity for Combivent – which expires in October 1999.

/S/
5/27/99
Robert J. Meyer, MD
Acting Director,
Division of Pulmonary Drug Products.

Division Director's Memorandum (addendum)

Date: Friday, March 16, 2001
NDA: 20-950
Sponsor: Dey Laboratories
Proprietary Name: Duoneb (albuterol sulfate 3.0 mg / ipratropium bromide 0.5 mg)
Inhalation Solution
PDUFA Goal Date: March 21, 2001

Introduction: This is a resubmission for this NDA for an inhalation solution for nebulization that combines ipratropium and albuterol in a single drug product. This combination has previously been approved as the Combivent Inhalation Aerosol, developed and marketed by another sponsor. This application is a 505(b)(2) application, referencing the sponsor's own albuterol inhalation solution and ipratropium inhalation solution products, but not the Combivent Inhalation Aerosol. Therefore, the sponsor had to support the safety and effectiveness of the combination of these two drug substances, including fulfilling the expectations under the combination policy.

CMC: Following our previous action, Dey is now proposing embossing of the LDPE vials, in addition to utilizing an overwrap to protect the product from egress of moisture and ingress of undesirable volatile substances. The CMC issues raised in the first review cycle appear to have been satisfactorily addressed (final CMC review is still pending). We are asking for a commitment to quantitate foreign particulates throughout the shelf-life and then modify their specification for this attribute accordingly.

Pharmacology/toxicology: all issues have been satisfactorily resolved, except for the preclinical qualification of the ^f While this qualification is necessary, we are willing to allow this to take place post-approval via a commitment.

Clinical / Stastical: There are no new safety issues identified and otherwise this product and its attendant labeling is clinically acceptable as supporting the safety and effectiveness of this combination product.

Labeling: We are still awaiting final labeling from the company in response to recent comments on the part of the agency, but if they incorporate our modifications, the labeling for this product should be acceptable. The name remains acceptable to OPDRA.

Conclusions: Assuming the final CMC review does not identify issues that would preclude it, this NDA will be given an approval action, once we have verification of commitments and final labeling.

/s/

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

file

JUN 4 1998

Division of Pulmonary Drug Products, HFD-570
CONSUMER SAFETY OFFICER REVIEW

Application Number: 20-950
Name of Drug: **Duovent (albuterol sulfate and ipatropium bromide) Inhalation Solution, 0.083% albuterol and 0.017% ipatropium**
Sponsor: **Dey Laboratories**
Submission Date(s): **May 28, 1998**
Receipt Date(s): **May 29, 1998**
User Fee Due Date: **May 29, 1999**

REVIEW

User Fee Information: paid \$256, 846 on January 12, 1998
User Fee # 3376
copy of check is included (volume 1.1, 1.00017)

NDA Summary Volume:

1. **Form 356h** is completed, signed, and dated in vol. 1.1
2. **Form 3397 (User Fee Cover Sheet)** is completed, signed, and dated.
3. **Cross-references** include 4 NDAs, 1 IND, and 5 DMFs.
4. **Establishment information** is listed on a separate page (vol. 1.1, 1.00008).
5. A **comprehensive table of contents** for the paper submission is given beginning on page 1.00026, volume 1.1. The **electronic table of contents** is also given beginning on page 1.00058, volume 1.1, and includes file names and contents and cross-references to the paper submission for each file for the entire NDA. Each NDA volume is subdivided by item numbers, and each item contains an **item-specific table of contents** as well.
6. An organizational description of the application is given in volume 1.1, beginning on page 1.00018.

7. No **patent information** is provided, but a certification of no existing patents on this formulation is included.
8. A **debarment certification and field copy certification** are provided in volume 1.1, beginning on pages 1.00011 and 1.00013.

Review Discipline Volumes:

1. Each review discipline has been provided with a copy of volume 1.1 and an electronic copy of the entire submission on compact disc.
2. Each review discipline is assigned a specific item number. There is an item-specific table of contents, list of tables, list of figures, and list of abbreviations at the beginning of each item.

General Information

1. A **debarment statement** certifies that Dey and its contractors have not been convicted on any crime or used any clinical investigator in the past, present, or future identified by the United States Food and Drug Administration on the recent debarment list.
2. The sponsor has applied for exclusivity for a period of 3 years from the date of approval of this application, pursuant to 505(j)(4)(D)(iii) and 505(c)(3)(D)(iii).
3. The entire submission was also submitted electronically on 1 compact disc.

Conclusion: The application can be filed from the administrative standpoint.

David Hilfiker
Project Manager

cc: Original NDA 20-950
HFD-570/Division files
HFD-570/Hilfiker
HFD-570/Schumaker

6-4-98

6/4/98

Memorandum of Telephone Facsimile Correspondence

Date: March 8, 2001

To: Peggy Berry
Dey L.P. Regulatory Affairs

Fax No.: 707-224-1364

From: David Hilfiker
Project Manager

Subject: CMC Information Request

of Pages: 3

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

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 827-1050 and return it to us at 5600 Fishers Lane, HFD-570, DPDP, Rockville, MD 20857.

Thank you.

March 8, 2001

Peggy:

The following is requested to further evaluate your NDA 20-950, DuoNeb. Please provide responses to these issues as soon as possible, and contact me at your earliest convenience to inform me of when you expect to have a response prepared to submit.

Also, as previously requested, you need to submit to the NDA the latest version of the embossing text for the vials, as you provided in the facsimile of February 28. If possible, provide a copy of that submission to me by facsimile to facilitate our review process.

I need to emphasize that the following are comments from the CMC review only. We may have further labeling comments to provide in the near future.

Your submission in response to these comments should include your commitment to conduct the requested studies as written, with specific proposed dates for submission of the protocol (where applicable), initiation of studies (where applicable), and submission of the final study report to fulfill the commitment (need for each). The following is requested from Dr. Kim, CMC Reviewer:

List of Chemistry Deficiencies and Comments

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]
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]
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 a revised version. [Comment 9.d]
4. The following comments pertain to foreign particulates [Comment 11.a]:
 - a). Since the container/closer system is the same, foreign particulates specifications for the DuoNeb should be identical to those for the AccuNeb. Justify/explain the discrepancy.
 - 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.
 - c). The updated stability data of the lots R301 and R324, made with _____

1

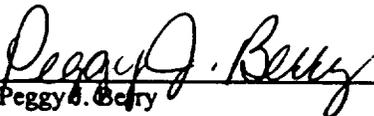
overwrap, indicate that the lots failed to meet "the particulate matter specification" even at time 0. Explain the cause(s) of failure. State the nature of particulate. [Amendment dated March 1, 2001]

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).
 - 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).
 - c). Provide an updated stability protocol and data that reflect all requested modifications.
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.
 - 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.
 - c). The embossing artwork [Fax dated February 28, 2001] is acceptable. Provide actual product samples as soon as possible.

PATENT INFORMATION/CERTIFICATION

In the opinion and to the best knowledge of Dey LP, there are no relevant patents that claim the drug on which investigations that are relied upon in this application for Dey Combination, albuterol sulfate/ipratropium bromide inhalation solution, were conducted or claim use of such drug.


Peggy J. Berry
Regulatory Affairs Manager
Dey LP
2751 Napa Valley Corporate Drive
Napa, CA 94558

EXCLUSIVITY SUMMARY for NDA # 20-950 SUPPL # _____

Trade Name DuoNeb Inh. Soln.

Generic Name 3.0 mg albuterol sulfate and 0.5 mg ipratropium bromide per 3 mL

Applicant Name Dey, L.P. HFD- 570

Approval Date March 21, 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 / X /

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 / / NO / /

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

NDA # _____
NDA # _____
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 #	<u>19-243</u>	<u>Proventil Inh. Soln.</u>
NDA #	<u>20-228</u>	<u>Atrovent Inh. Soln.</u>
NDA #	<u>19-773</u>	<u>Ventolin Inh. Soln.</u>

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 / ___ / NO / X /

- (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 / ___ /

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 / X /

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-024

Investigation #2, Study # _____

Investigation #3, Study # _____

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 /___/

Investigation #3 YES /___/ NO /___/

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 / <u>X</u> /
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

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 # <u>1</u> ,	Study # <u>DL-024</u>
Investigation # <u> </u> ,	Study # _____
Investigation # <u> </u> ,	Study # _____

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 # _____ / YES / X / ! NO / ___ / Explain: _____
 !
 !
 !
 !

Investigation #2
 IND # _____ YES / ___ / ! 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: _____

Signature of Preparer
Title: _____

Date

Signature of Office of Division Director

Date

CC:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

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

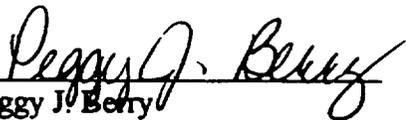
/s/

David Hilfiker
3/21/01 01:53:11 PM

Robert Meyer
3/21/01 01:57:00 PM

DEBARMENT CERTIFICATION

I certify that neither Dey Laboratories nor any of its contractors affiliated with this application have 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 section 306 (a) or (b) of the Generic Drug Enforcement Act of 1992.


Peggy J. Berry
Regulatory Affairs Project Manager
Dey Laboratories
2751 Napa Valley Corporate Drive
Napa, CA 94558

Date: 5/12/98

RECORD OF TELEPHONE CONVERSATION

Date: June 12, 1998
Project Manager: Hilfiker
Subject: Request for samples
NDA: 20-950
Sponsor: Dey Laboratories
Product Name: Duivent Inhalation Solution

Dey Labs submitted an original NDA for Duivent (albuterol sulfate and ipratropium bromide) Inhalation Solution on May 28, 1998. The user fee goal date is May 29, 1999.

I contacted the sponsor to request 2 pouches of sample (10 vials total) for the CMC reviewer. No specific batch numbers were requested. The sponsor agreed to send the requested samples for Duivent as well as for its pending NDA for Accuvent Inhalation Solution, submitted on March 30, 1998.

CS */S/*
6-12-98

David Hilfiker, Project Manager

cc: NDAs 20-949 and 20-950
HFD-570/Division File
HFD-570/Hilfiker
HFD-570/Schumaker
HFD-570/Kim

CS
6/15/98

Minutes of Industry Meeting

Date: June 17, 1997
Time: 1:30 p.m. to 2:30 p.m.
Place: Parklawn Conference Room ☒ ☒
IND: []
Sponsor: Cato Research for Dey Laboratories
Drug: albuterol sulfate and ipratropium bromide inhalation solution
Meeting Type: PreNDA

FDA Attendees

J. Lindsay Cobbs, R.Ph.	Project Manager
Dale Conner, Pharm.D.	Team Leader, Biopharmaceutics and Clinical Pharmacology
James Gebert, Ph.D.	Biometrics
John K. Jenkins, M.D.	Division Director
Robert Meyer, M.D.	Team Leader, Clinical
Linda Ng, Ph.D.	Chemistry Reviewer
Mary Purucker, M.D., Ph.D.	Clinical Reviewer
Hilary Sheevers, Ph.D.	Team Leader, Pharmacology
Denise Toyer, R.Ph.	Project Manager
Virgil Whitehurst, Ph.D.	Pharmacology Reviewer

Dey Laboratories

Allan S. Kaplan, Ph.D.	Vice President of Technology Affairs
Randall E. Miller, Ph.D.	Director Product Development

Cato Research Ltd.

Allen Cato, M.D., Ph.D.	President and CEO
William P. Coleman, Ph.D.	Consulting Statistician
Diana Fordyce, Ph.D.	Clinical Research Scientist and Regulatory Specialist
Beth Glenn, B.S.	Project Coordinator
Michele Jumper, Ph.D.	Clinical Research Scientist
Steven e. Linberg, Ph.D.	Vice President, Clinical Development
Sarah Middleton, B.S.	Project Manager
Carl Sigel, Ph.D.	Director, Research and Development
Thomas Soeder, M.S.	Senior Statistical Programmer
Lynda Sutton, B.S.	Senior Vice President, Regulatory Affairs and Project Planning

Background

Cato Research on behalf of Dey Laboratories requested a preNDA meeting. Refer to background package, serial number 014, dated June 2, 1997.

Objective

1. Discuss the regulatory issues relating to a 505(b)2 application.
2. Obtain input from the Pulmonary Division on the proposed NDA content.

Chemistry

A chemistry meeting is scheduled for August 28, 1997 to discuss in detail the chemistry questions. Dr. Ng noted that the March 22, 1996 deficiency letter listed chemistry recommendations. She made the following suggestions after completing the review of the limited submission.

Drug Substance

The submission noted that Dey planned to use USP and EP specifications. Dr. Ng stated the USP and EP specifications are unacceptable and the specifications should be updated.

Drug Product

The following specifications should be determined for the drug product.

- Quantitative color test, e.g., APHA color;
- Volume delivery, mean and individual
- Extraneous particulates
- Content uniformity-release (it is acceptable to use weight since the formulation is a true solution)
- Assay per container (due to the water loss, we recommend that the assay be conducted on the container instead of per ml)

Stability

Only one batch is mentioned in the submission. Three batches for six months under 40°/10-20% RH and 25°/40% RH are required. Refer to March 22, 1996 letter. The expiration dating period will be based on the data.

Special Studies

Studies on extractable, temperature cycling and photostability should be conducted. The rate of water loss and wall thickness should also be evaluated.

Other Clarifications

Dey plans to market a 3 mL container with a paper label. Each foil package will contain 5 nebulers. The package will not be filled. They have no plans to use an overwrap. The sponsor is aware that albuterol degrades but they will present data which shows the stability of their product without overwrap. The Division is concerned about

the degradation properties of albuterol and the paper label which Dey plans to use. We will discuss these two issues further at the CMC meeting in August.

Pharmacology

There are three preclinical issues which must be addressed regarding Duvoent®.

1. Dey must show that the combination of albuterol and ipratropium does not increase the toxicity seen with either agent separately. We are especially interested in the combination product's effect on the cardiovascular system. This information may be provided through:
 - a. an extensive literature search (assuming adequate data are available in the published literature); or
 - b. a 30 day study using two animal species (one rodent and one nonrodent) comparing each individual agent and the combination product.
2. The proposed formulation contains EDTA as a chelating agent. EDTA is known to be a bronchoconstrictor. Dey must provide data that shows inhalation of this agent is safe. This information may be provided through:
 - a. an extensive literature search (assuming adequate data are available in the published literature); or
 - b. a six month inhalation study in one species (the most appropriate animal species).
3. The labeling should include the most current information available regarding the toxicity of the combination product.

When Dey submitted the original ANDA for albuterol they believed that EDTA was a qualified excipient. They will have to look at their original data to determine how they came to that conclusion. Dey wanted to know if the Division's toxicity concerns are diminished by the numerous years that albuterol and Atrovent have been marketed. Dr. Jenkins explained that these data only come from the adverse reporting system and it reports data on the individual products which may or may not be administered together. This system does not provide long term toxicity (carcinogenicity, etc.) data for the combination product.

If the data cannot be determined through a literature search, the Division will work with Dey laboratories to develop an adequate toxicology protocol.

Biopharmaceutics and Clinical Pharmacology

Dey should conduct a literature search to determine if one agent has any affect on the other agent when given as a combination product in humans. If this information is not found in the literature search, a study needs to be conducted. We are aware that it would be difficult to obtain ipratropium serum levels and note that the dose might have to be increased to 3 or 4 times the normal dose to get a discernible concentration. Our main pharmacokinetic concerns are for albuterol. The assays currently available are more specific and it should not be difficult to obtain good results.

Clinical

The FDA has approved NDAs based on a single adequate and well-controlled study, but the Division encourages sponsors to conduct two adequate and well-controlled clinical studies. If Dey plans to submit the NDA with only one study, the Division would like Dey to conduct an adequate literature search to obtain additional data to support the combination use of albuterol and ipratropium in the treatment of COPD. There is no placebo arm in Dey's trial. However, if the combination product proves superior to each one of the components, and each component is an approved product, the current design is acceptable. This will be a review issue, however.

Biometrics

Please clarify the following two concerns. Address the possibility of side effects carried over into the parallel portion of the study affecting the comparison of side effect profiles during the parallel phase. When the NDA is submitted please explain and provide references for the analyses. Upon preliminary review, the SAS data files appear adequate.

Regulatory

Currently this application does not qualify as a 505(b)1 application. The sponsor of a 505(b)1 application must conduct or have right of reference to all of the required studies needed for submission and approval. To qualify for 505(b)2 application, Dey must list the reference product(s) that the application is based on. Additionally, the applicant must certify that: 1) no patents have been filed

for the reference product; 2) the patent on the reference product has expired or will expire including the dates; or 3) the patent is invalid or will not be infringed upon by the marketing of the proposed NDA. This certification must be filed with the original application.

Dey plans to submit this application as a 505(b)2. Three different pathways may be taken to be submitted as a 505(b)2.

1. Obtain right of reference to the Combivent NDA from Boehringer. This would enable Dey to use any data submitted in the Combivent NDA. Dey needs to receive authorization from Boehringer for right of reference.
2. Submit data via literature search for preclinical, biopharmaceutics and clinical in addition to data from the actual study conducted.
3. Dey may reference Combivent but can only receive tentative approval (TA). Once the exclusivity has expired then Dey's NDA could receive final approval.

Currently Dey plans to use Atrovent and albuterol as the reference products for this NDA. They have not decided if they will reference Combivent. Combivent has exclusivity until October 1999.

Conclusions

1. The Division's concern with lack of overwrap and the paper labeling issues will be discussed in detail at the CMC meeting. Dey will review the CMC recommendations presented and ensure that their products meet the specifications. Further CMC information will be provided prior to the August meeting.
2. A literature search must be conducted to show the safety of the combination product and EDTA when administered by inhalation as part of the preclinical section. If acceptable literature cannot be found to support safety, Dey will contact the Division with proposed study protocols for review.
3. Dey will conduct a literature search to show the pharmacokinetics (Pk) of the combination product in humans. If data unavailable, Dey will consider doing PK study.
4. Dey will conduct a literature search to provide additional clinical support for the combination use of albuterol and ipratropium in the treatment of COPD.

These data will be reviewed by the Division and may be the basis to obviate the need for a second adequate and well-controlled clinical trial.

5. The Division will request a legal opinion on Dey's request to submit this application as a 505(b)2 application and define the requirements for the submission.

Denise P. Toyer
Project Manager

Post Meeting Follow-up

Donald Hare, from the Office of Generic Drugs, expressed his opinion that Dey's 505(b)2 new drug application could not be approved pending expiration of Boehringer Ingelheim's exclusivity for Combivent even if Dey does not reference the Combivent NDA and even if Dey provides data in support of the combination product from the literature and/or their own studies. The sponsor was informed of this possibility on July 16, 1997 by Ms. Denise P. Toyer, Project Manager.

Memorandum

To: NDA 20-950
From: Robin A. Huff, Ph.D., Acting Pharmacology Team Leader
Date: April 16, 1999
Re: Team Leader NDA Summary

JS

4-16-99

Overall Pharmacology/Toxicology Recommendation - Approvable

Product Summary

Duovent is an inhalation solution of albuterol, a beta-2-agonist, and ipratropium, a muscarinic antagonist, intended for treatment of chronic obstructive pulmonary disease (COPD). Each vial contains 2.5 mg albuterol and 0.5 mg ipratropium. Up to six vials may be administered per day via a nebulizer, which results in a daily dose of 0.3 mg/kg albuterol and 0.06 mg/kg ipratropium for a 50 kg person. This NDA was a 505(b)(2) application.

Outstanding Issues

The only outstanding issues are labeling revisions (refer to Dr. Whitehurst's April 7, 1999 review). The labeling revisions suggested by Dr. Whitehurst apply recent improvements in albuterol product labeling to Duovent labeling. However, these changes result in a labeling format that is no longer similar to Combivent labeling. The review team will need to decide whether to parallel Combivent labeling or use the proposed revisions.

Summary of Significant Preclinical Studies

In response to the Division's recommendation, the sponsor evaluated the toxicity of albuterol and ipratropium in combination by performing 30 day studies in rats and dogs. The primary purpose of these studies was to determine if the cardiotoxicity caused by albuterol was potentiated by ipratropium. Results of both studies, which used subcutaneous administration, indicate that ipratropium does not potentiate the cardiotoxicity of albuterol.

Extensive studies have been conducted to support previous approvals of the individual active components of Duovent, albuterol and ipratropium. For albuterol, as for 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 an 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 of albuterol are summarized in product labeling.

For ipratropium, classic indications of anticholinergic activity such as mydriasis, xerosis and tachycardia were produced at high systemic exposure; however, ipratropium was poorly absorbed after inhalation, and thus produced minimal inhalation toxicity. Reproductive toxicity studies performed in mice, rats and rabbits indicated that ipratropium was not teratogenic. However, ipratropium did impair fertility and increase resorptions in rats given oral doses that are high multiples of human inhalation doses. Ipratropium was not genotoxic as assessed in an Ames test, a mouse dominant lethal test, a mouse micronucleus test and a hamster chromosomal aberration test. Ipratropium was not carcinogenic in 24 month studies performed in mice and rats. Data relevant to reproductive toxicity, genotoxicity and carcinogenicity of ipratropium are summarized in product labeling.

cc:

/HFD-570 Division file

/Huff

/Hilfiker

JUN 23 1998

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
DIVISION OF PHARMACEUTICAL EVALUATION II

Date: June 23, 1998

To: Director, Mei-Ling Chen, Ph.D. (HFD-870)
Deputy Director, Mr. John Hunt (HFD-870)
Team Leader, Ramana Uppoor Ph.D. (HFD-870)

/S/

.06/23/98

From: Tien-Mien Chen, Ph.D. (HFD-870)

/S/

06/23/98

RE: Filing Meeting for An Original NDA 20-950 (Duvent Inhalation Solution;
albuterol sulfate and ipratropium bromide) Code: 3S

SYNOPSIS:

On 05/28/98, Dey Laboratories submitted an original NDA 20-950 for Duvent Inhalation Solution (albuterol sulfate 0.083% and ipratropium bromide 0.017% per 3 ml vial). Each Duvent vial will provide 2.5 mg of albuterol and 0.5 mg of ipratropium in an isotonic, sterile, aqueous solution. The sponsor is seeking approval for the treatment of bronchospasm associated with COPD in patients requiring more than one bronchodilator. The recommended dosing regimen is one vial QID with up to 2 additional doses allowed per day if needed. Please see the package insert in Attachment 1 for details.

Submitted under Item 6, Human pharmacokinetics (PK)/Bioavailability (Bio) section, of NDA 20-950 was one PK study No. DL-031; double-blind, randomized, 2x2 crossover, single-dose (2 vials), drug-drug interaction study (1 mg ipratropium on 5 mg albuterol only) in 15 male and female volunteers. Inhalation Solution containing albuterol sulfate only was used as the reference. Plasma levels of albuterol only and recovery of both albuterol and ipratropium excreted in urine were obtained. Furthermore, upon the Agency's request in a pre-NDA meeting dated 06/17/97, a summary report from 56 published articles from literature was also submitted. For the clinical program, only one pivotal clinical trial, No. DL-024 was conducted. The formulation/batch no. used in the human PK/Bio and clinical studies was the same and it is the to-be-marketed formulation manufactured using the commercial equipment (25% of what a full-scale production batch size will be). The assay validation report was provided. Finally, package insert, Item 6: Human PK text, and Study No. DL-031 (final study report, protocol, data listings and tablets, and PK sample data) were submitted in an electronic format on a CD-ROM.

RECOMMENDATION:

NDA 20-950 for Duovent Inhalation Solution (albuterol sulfate 0.083% and ipratropium bromide 0.017%) that was filed by Dey Labs. has been briefly reviewed by Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE II). OCPB/DPE II is of the opinion that NDA 20-950 is acceptable for filing.

COMMENT: (Need not be sent to the sponsor)

In PK study No. DL-031, no treatment arm for ipratropium alone was employed. Therefore, comparisons of urinary recovery of ipratropium from albuterol and ipratropium combination (Duovent) vs. ipratropium alone is not available. Furthermore, the study ideally should have been conducted in COPD patients.

**APPEARS THIS WAY
ON ORIGINAL**

cc: HFD-870 (T.M. Chen, R. Uppoor, J. Hunt, M.L. Chen).

Hilfiker

RECORD OF TELEPHONE CONVERSATION

NDA NUMBER: #20-950

DATE: 30 April, 1999

INITIATED BY: APPLICANT FDA

FIRM NAME: Dey Laboratories

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD:

Peggy Berry (Dey Labs), Stephen E. Lindberg, Ph.D.
(Collaborative Clinical Research, Inc; Cato Reseach)

TELEPHONE NUMBER: (707)224-3200 x4750

The following clarifications of NDA #20-950 (albuterol-inpratropium combination solution) were requested of Peggy Berry in a telephone conversation on 4/27/99.

Q1: The protocol states that "AE's were considered either possibly related or unrelated to the product" [23:209]. The protocol states that the clinical investigator will not participate in classifying AE's for either severity or causality and that these classifications will be performed by the sponsor's clinical monitor or causality will be classified by the Drug Safety Committee if the AE is an SAE [24:469]. Table 3.6.3 is the summary of related treatment emergent AE's by study drug, including events judged by the investigator to be 'possibly' or 'probably' related to the study drug [24:378-81]. How many categories of AE causality were used and who assigned severity and causality to the cases?

A1: The protocol is misleading. Sample case report forms were filled out by the clinical investigator (CI) and have the causality category 'possibly/probably related' [24:524]. In practice, the CI judged causality and severity and recorded these on the CRF. SAE's were a special case where the monitor reviewed the CI's assessment of severity and causality was assigned by the Data Safety Committee. Dr. Lindberg provided assurance that in no case was the severity assigned by the CI rendered less related by monitor or committee.

Q2: Are there any more extensive narratives of deaths and early discontinuations due to AE's than the tabular summary [29:2297]?

A2: Yes, reference for beginning of narratives [29:2302].

Q3: There are non-matching patient counts in the organizational box chart and the demographic variable reports for the crossover phase [24:437, 260-5].

A3: A total of 647 patients were included in both parts of the primary efficacy analysis (crossover phase) and 663 were available for either of the two primary efficacy comparisons (AI vs. A and AI vs. I) [23:98, 226-7].

The following are more requests for location of information addressed to Peggy Berry during this telecon that she will answer in the next telecon on Monday at 1300 hours, 5/3/99.

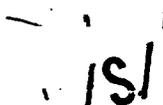
Qa1: Efficacy measures for the parallel phase were carried out on Day 84 [23:102, 24:468]. Are similar tabulations by treatment available for Days 56 and 70?

Qa2: Extra aerosol nebulizations or albuterol by MDI were to be used for rescue treatments [24:455-6, 462]. Are there any tabulations of rescue medication use by treatment and phase?

Qa3: Temporary withdrawal for an exacerbation is covered in the protocol [24:463]. Is there a listing of how many patients were temporarily withdrawn from the crossover phase because of exacerbations by patient group and at what point in the study they were allowed to reenter?

Qa4: Lab values and ECG's were done at baseline and at study termination and clinically significant values and changes were to be reported as AE's [24:436]. Are actual lab values or ECG parameters available for review? Labs are presented by variable and drug as means for baseline and final values [24:417-24].

Qa5: I could find no reference to timing, procedure or recording of vital signs and weights in the protocol, but they were reported in the study results. Clinically significant values or changes in vital signs and weights were reported as AE's, though there were none [23:142]. Is there a protocol reference for weight and vital sign collection and are actual values reported somewhere in the NDA?


Raymond F. Anthracite, M.D.
Medical Review Officer

cc:
IND #20-950
HFD-570/Division File
HFD-570/Medical Reviewer/Anthracite
HFD-570/PM/Hilfiker

Hilfiker

RECORD OF TELEPHONE CONVERSATION

NDA NUMBER: #20-950

DATE: 3 May, 1999

INITIATED BY: APPLICANT FDA

FIRM NAME: Dey Laboratories

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD:
Peggy Berry (Dey Labs)

TELEPHONE NUMBER: (707)224-3200 x4750

The following clarifications of NDA #20-950 (albuterol-inpratropium combination solution) were requested of Peggy Berry in a telephone conversation on 4/30/99 and answers were provided today.

Qa1: Efficacy measures for the parallel phase were carried out on Day 84 [23:102, 24:468]. Are similar tabulations by treatment available for Days 56 and 70?

Aa1: They can be found in Table 2.3 [24:278-296]. Table 2.4 gives the change in trough FEV_{1.0} from Day 28 to Day 84 [24:297]. Table 2.5 shows the trough FEV_{1.0} for each visit by each of the six crossover sequences [24:298-9].

Qa2: Extra aerosol nebulizations or albuterol by MDI were to be used for rescue treatments [24:455-6, 462]. Are there any tabulations of rescue medication use by treatment and phase?

Aa2: No recording of rescue medication use was made.

Qa3: Temporary withdrawal for an exacerbation is covered in the protocol [24:463]. Is there a listing of how many patients were temporarily withdrawn from the crossover phase because of exacerbations by patient group and at what point in the study they were allowed to reenter?

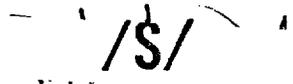
Aa3: Patients restarted at beginning of dosing interval from which they withdrew and an exacerbation was recorded as an AE. Therefore, patients with an exacerbation who completed the entire protocol must have reentered it. However, those who had an exacerbation but did not complete the phase or the protocol may have quit for another reason.

Qa4: Lab values and ECG's were done at baseline and at study termination and clinically significant values and changes were to be reported as AE's [24:436]. Are actual lab values or ECG parameters available for review?

Aa5: Labs were presented by variable and drug as means for baseline and final values [24:417-24]. ECG data exists only as AE's.

Qa5: I could find no reference to timing, procedure or recording of vital signs and weights in the protocol, but they were reported in the study results. Clinically significant values or changes in vital signs and weights were reported as AE's, though there were none [23:142]. Is there a protocol reference for weight and vital sign collection and are actual values reported somewhere in the NDA?

Aa6: Appendix 11.5.1.1 shows heights and weights, one set for each patient probably done as a part of the screening exam, but they aren't in the protocol and BP and pulse aren't in either the protocol or a tabular summary [25:617-906].


Raymond F. Anthracite, M.D.
Medical Review Officer

cc:
NDA ~~IND~~ #20-950
HFD-570/Division File
HFD-570/Medical Reviewer/Anthracite
HFD-570/PM/Hilfiker

RECORD OF TELEPHONE CONVERSATION

Date: June 12, 2000
Project Manager: Hilfiker
Subject: Clarifications to AE letter
NDA: 20-949 and 20-950
Applicant: Dey Laboratories
Product Name: AccuNeb and DuoNeb Inhalation Solutions (respectively)

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, and 20-950, DuoNeb (albuterol sulfate and ipratropium bromide) Inhalation Solution, on June 2, 2000.

DEY sent a request for a teleconference via June 9, 2000, facsimile correspondence (attachment 1), for clarification of some of the comments in the June 2, 2000, DuoNeb letter. 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 _____ 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 provide the data to ensure that the formation of _____ does not increase with time and that it remains below the proposed specification, _____ % w/w. If*

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

- e. With reference to the chromatogram provided with method [redacted], specify the peak(s) eluting prior to unknown #1 and the unresolved shoulder peak co-eluting with unknown #1 (RT 2.352, 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 (e.g., [redacted] 0 – 10 min).

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

Dr. Kim clarified that comment 1.d. applies to DuoNeb method [redacted]. Comment 1.e. does not apply for DuoNeb, and should only be addressed in the AccuNeb response.

2. The specification ([redacted] % w/w) proposed for APO-ipratropium bromide in the drug substance can not be finalized until it is qualified at an appropriate level. (comment 2.b.)

Dr. Kim emphasized that [redacted] % is beyond the qualification threshold of [redacted] % w/w for drug substance impurities. Dr. Sun added that APO-ipratropium 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 ipratropium 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.

[redacted]

9. *The following comments pertain to the potential leachables of the proposed packaging components (LDPE vial; paper label: adhesive overlacquer label stock, inks; and LLDPE overwrap) into the drug product.*
- a. *Comparison of the chromatographic data provided for the placebo samples within themselves (LDPE vials containing acidified water with and without self-adhesive paper labels, Figures 1-18, pp. 0196-0213/Vol. 6) and with the drug product samples (Figures 19-32, pp. 0214-0227) clearly show the presence of several additional peaks, most likely due to leachables. These peaks are not observed in the control samples (acidified water) and appear to increase on storage with time and temperature. These chromatographic data are inadequate in terms of chemical identity and quantitation of these leachables, and therefore do not assure the absence of significant leachables in the drug product. As requested earlier, identify, characterize, quantify and qualify these potential leachables individually. Relate each leachable to the adequately characterized and quantified extractable profile of the corresponding packaging components.*

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 paper labeled vials and preprinted overwrap. Recent work has shown that the vendor's process of printing and subsequently rolling the preprinted overwrap causes the internal overwrap surface to become contaminated with other solvents used in printing. Therefore, Dey plans to use overwrap which is not preprinted. 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.

DEY asked if 505(b)(2) regulations can be used to refer to product that was approved by FDA with an overwrap, and the identical overwrap is used with DuoNeb. Dr. Meyer stated that further internal discussions regarding 505(b)(2) regulations and how they apply to packaging components are necessary before the Division can respond to this question.

DEY asked if the possible qualification of leachables derived from the overwrap can be conducted as a Phase 4 commitment. The Division did not provide a response, but Dr. Meyer indicated that he was uncomfortable with the amount of information that DEY was asking to supply post-approval.

Dr. Shah emphasized the need to identify and quantify potential leachables from overwrap materials prior to approval, because this information is necessary to ensure batch-to-batch consistency of quality after approval. Due to the lack of regulation of DMF holders, Dr. Shah noted that the composition of the overwrap can change (and so the leachable/extractable profile of the overwrap can change) without prior notice or opportunity for review. Because of this, it will be necessary for DEY to monitor the extractable profile for each shipment/batch of incoming overwrap material (foil-laminate). DEY asked if a profile of volatile materials could be supplied in place of an extractable (non-volatile) profiles to ensure batch-to-batch consistency of the overwrap. Dr. Shah indicated that a linkage between the extractable and leachable profiles must first be established before a volatile profile could substitute for a nonvolatile profile as a quality control test. However, with any change in overwrap composition, the extractable-leachable linkage for the drug product would have to be re-established.

9. *The following comments pertain to the potential leachables of the proposed packaging components (LDPE vial; paper label: adhesive overlacquer label stock, inks; and LLDPE overwrap) into the drug product.*
- e. *If debossing/embossing of the LDPE vials is chosen instead of the self-adhesive paper labels, only identification and qualification of the extractables/leachables arising from the LLDPE overwrap need be addressed.*

Since we agree to emboss vials and not use paper labels, we would like to confirm that identification and qualification need be addressed only for the extractables and leachables arising from the overwrap.

Dr. Shah reminded DEY that extractables and leachables need to be identified, quantified, and possibly qualified from the LDPE vial itself in addition to the overwrap.

10. *The following comments pertain to LLDPE foil-laminate overwrap*
- b. *Demonstrate with appropriate supportive data that the proposed extraction conditions in water (70°C, 24 hrs, method p. 0176/Vol. 5) are*

suitable (especially with extraction time) to provide a consistent amount of non-volatile extractable from the foil-laminate overwrap. Revise method accordingly and resubmit the updated method. In order to assure consistent quality of the foil-laminate, identify and quantify the extractable profile of the non-volatile residue obtained from the foil-laminate overwrap by method using sensitive analytical techniques. Based on the extractable profile of non-volatile residues, establish acceptance criteria for non-volatile residues per foil-laminate overwrap, supported with adequate data. The proposed specification, mg for non-volatile residues per pouch, is not acceptable.

If Dey increases the extraction time (e.g., increase to 48 or 96 hours at 70°C), so that a significant and consistent amount is extracted, and sets a specification limit in mg, will that be an acceptable extractable profile to be used as release criteria for the foil-laminate overwrap? Also, per your request, Dey plans to use a more sensitive method, for non-volatile residue.

Dr. Shah stated that DEY must first identify the optimal extraction conditions for the overwrap. Using the optimal conditions, DEY should separate and identify compounds that were extracted.

If the new method confirms a total amount of extractables in the microgram range, instead of the milligram range that has been shown with the current gravimetric method, DEY asked if extractables would still have to be individually identified and quantified. Dr. Poochikian stated that if total extractables are in the microgram range, and if leachables are found to be less than total extractables, then their proposal may be entertained.

ADDITIONAL DISCUSSION

DEY referred to the section of their meeting request entitled "BACKGROUND INFORMATION" (see attachment 1).

- 2. With the exception of FDA's comment 3d, for which we need clarification, Dey intends to agree without further comment to the FDA's proposed specifications – where a specific value was provided – in comments 1a, 2, 3b, and 12b. In addition, we agree to tighten specifications as requested in comments 1b, 4b(4), and 4c based on available data and a statistical 3 standard deviation approach.**

DEY asked for FDA's agreement that the proposed statistical 3 standard deviation approach is acceptable. Dr. Poochikian stated that use of this approach is dependant on the data. If the data are highly variable and produce a large standard deviation, then this approach is not acceptable.

Dr. Poochikian asked DEY if they have characterized any *in vitro* properties of the nebulizer(s)

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

- DEY requested that FDA allow qualification of ipratropium bromide 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 ipratropium than their reference product (Atrovent). This is analogous to the situation for qualification of a albuterol impurity in DEY's pending AccuNeb and DuoNeb applications.
- 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, instead of having to characterize the extractables and leachables of the overwrap materials in their products. 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 two 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 and 20-950
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

RECORD OF TELEPHONE CONVERSATION

Date: July 18, 2000
Project Manager: Hilfiker
Subject: Use of Paper Labels on Drug Product Overwrap
NDA: 20-949 and 20-950
Sponsor: Dey L.P.
Product Name: AccuNeb and DuoNeb Inhalation Solutions

Both applications are pending. Approvable letters were issued for NDA 20-949 on June 6, 2000, and for 20-950 on June 2, 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-laminate 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

NDA 20-949 and 20-950
Page 2 of 2

wait for the Division's response to determine what information is needed for their response to the action letter.

David Hilfiker
Project Manager

Cc: Original NDAs 20-949 and 20-950
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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RECORD OF TELEPHONE CONVERSATION

Date: July 23, 1999
Project Manager: Hilfiker
Subject: Discussion of AE letter comments
NDA: 20-949 and 20-950
Sponsor: Dey Laboratories
Product Name: Accuneb (albuterol) and Duoneb (albuterol/ipratropium)

NDA 20-949, albuterol sulfate inhalation solution, and 20-950, albuterol sulfate/ipratropium bromide inhalation solution, were submitted by Dey Laboratories as 505(b)(2) applications and were issued approvable actions on March 30 and May 28, 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.*

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

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 beclomethasone dipropionate and ipratropium bromide, 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.

Dey referred to a previous commitment to identify leachables using method and acidified water as a model solvent and matrix representative of the drug product. The testing will continue for 18 months. However, the applicant wishes to rely on information supplied in a DMF along with stability testing of finished product vials with pre-made paper labels 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 used 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 (adhesives, paper, overlacquer, inks, etc.) used in the manufacture of the self-adhesive paper labels.
2. Identify and establish an extractable profile of the paper label and its components (adhesive, paper, overlacquer, inks, etc.) in suitably discriminating solvents for lot-to-lot quality assurance of incoming paper labels.
3. Identify (if possible) all leachables from the container-closure system (LDPE container and self-adhesive 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 to screen for various general classes of compounds 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 resin 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 acidified water may not be the most discriminating solvent to separate all possible extractable and leachable compounds, and the applicant should consider testing several solvents with varying polarity to identify which is the most discriminating.

23. You have requested specifications _____% for two 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 these two impurities to _____% w/w.

The applicant stated that the first impurity above has been lowered to _____% in the drug substance, but that the second impurity _____ (compound) 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 _____ down to _____%. 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 was proposing to use the data from Ventolin because of the 505(b)(2) status of their application in reference to Ventolin as the reference product. The applicant asked the Division to consider applying the 505(b)(2) regulations to allow them to reference the innovator product in order to qualify impurities.

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

NDA 20-949 and 20-950

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in policy would be communicated to the applicant.

David Hilfiker
Project Manager

Cc: Original NDAs 20-949 and 20-950
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

RECORD OF TELEPHONE CONVERSATION

Date: August 16, 2000
Project Manager: Hilfiker
Subject: Information Needed to Support Altered Paper Label Plans
NDA: 20-949 and 20-950
Sponsor: Dey L.P.
Product Name: AccuNeb and DuoNeb Inhalation Solutions

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 use of paper labels directly on the LDPE vials. Rather than address the deficiencies, Dey has proposed attachment of paper labels to the outside of the overwrap, and embossing 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 Vibhakar Shah	Project Manager CMC Reviewer
Dey Participants:	Peggy Berry Imtiaz Chaudry Salisa Poon	Regulatory Affairs Scientific Affairs 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 to prevent ingress of volatile compounds from the paper label into the drug product. FDA

NDA 20-949 and 20-950

Page 2

reminded Dey that the DMF for the foil-laminate 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 for volatile/non-volatile residues, 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

 8-25-00

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

Cc: Original NDAs 20-949 and 20-950
HFD-570/Division files
HFD-570/Hilfiker
HFD-570/Shah/8-24-00
HFD-570/Kim
HFD-570/Poochikian

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: Accuvent and Duovent (respectively)

BACKGROUND:

NDA 20-949 was submitted by Dey Labs on March 27, 1998, for Accuvent (albuterol sulfate) Inhalation Solution. NDA 20-950 was submitted by Dey Labs on May 28, 1998, for Duovent (albuterol sulfate and ipratropium bromide) Inhalation Solution. A problem identified with both applications in the pre-NDA phase was the presence of _____ appearing as an impurity in the stability samples over time. _____ is postulated not to be a breakdown product of albuterol, but rather a leachable by-product of one of the packaging components.

The applicant proposed a change in the overwrap used for the packaging of both products as a possible solution to eliminate _____ (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 LLDPE overwrap to support approval of the NDA?*

Dey proposes to conduct stability testing on one lot of Duovent and on one lot each of 0.042% and 0.021% Accuvent to support NDA approval. Longer term stability studies of the products in the LLDPE overwrap would be initiated following process validation (currently scheduled for January 1999), using 3 lots of each product and strength.

FDA:

- a. A minimum of 6 months 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 each of Duovent and 0.042% and 0.021% Accuvent can be used in stability studies for NDA approval. Please clarify what types of batches will be used to generate stability samples.

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

- c. The proposal to conduct long-term stability studies using 3 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 form/fill/seal and packaging process will be validated for commercial production by conducting 3 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 3 months of stability? Following 3 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 3 and 6 months stability data with reference to the user fee goal date of March 30, 1999.

Dey: 3 months data would be available in December. 6 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 LLDPE 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 self-sticking paper labels. Likewise, [one of the components used in the adhesive, may leach into the drug product under normal storage conditions. Have you considered alternative methods to using a paper label, such as embossing the vial?

Dey: Yes, we have considered embossing. 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 plastic label may be explored.

You may also consider embossing the content of the label onto a plastic appendage (i.e. plastic tab) 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 linear low density polyethylene (LLDPE).
- (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 (e.g., [] from the proposed overwrap into the drug product.

NDA 20-949 and 20-950
Page 4

David Hilfiker
Project Manager

Attachment: August 3, 1998, fax

cc: Original NDAs 20-949 and 20-950
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