



25 January 2007

Food and Drug Administration
Center for Drug Evaluation and Research
Badrul Chowdhury, MD, PhD, Division Director
Division of Pulmonary and Allergy Drug Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: New Drug Application 22-007/A011
Formoterol Fumarate Inhalation Solution, 20 mcg/2 mL
Response to FDA Mid-Cycle Review Comments

Dear Dr. Chowdhury,

Dey is responding to the Agency's facsimile dated 13 December 2006 containing Mid-Cycle review comments and requests for information. As requested by the Agency, Dey is providing the following information with this amendment:

- i) revised Package Insert and annotated Package Insert that includes a Boxed Warning (FDA comment 1)
- ii) Medication Guide and annotated Medication Guide (FDA comment 1)
- iii) Pharmacovigilance Plan and commitment to conduct the requested safety study (FDA comment 2)
- iv) methods for handling of missing data for Studies 201-065, DL-052 and DL-057 (FDA comment 4a)
- v) the numbers of subjects with progressively missing hourly visits, per visit and treatment group for trial 201-065 (FDA comment 4b)
- vi) sensitivity analyses of the primary endpoint for trial 201-065 using various imputations of missing data (FDA comment 4c)
- vii) summary of pulmonary function testing for the open-label period of study DL-059 (FDA comment 5).

Dey is requesting that the Agency reconsider its request for sensitivity analyses for the dose-ranging studies DL-052 and DL-057 based on the following:

25 January 2007

Badrul Chowdhury, MD, PhD, Division Director

Page 2

- In trial DL-052 missing FEV1 data was imputed with pre-dose values as requested by the Agency in 4(c) and FEV1 AUC values were not standardized by proportions of time less than 12 hours. In addition, the lowest dose in this trial, 40 mcg/2 mL, is twice that of the proposed marketed FFIS dose 20 mcg/2 mL.
- Results from the original analyses of trial DL-057 that included 5 doses of formoterol fumarate (2.5 – 40 mcg) showed the FFIS 20 mcg dose was superior to placebo and comparable to Foradil 12 mcg. Based on this information, the Agency agreed that FFIS 20 mcg dose was appropriate for continued development in Phase III (End of Phase II Minutes 02 April 2004). The results from the pivotal trial 201-065 demonstrated the clinical and statistical superiority of the FFIS 20 mcg/2 mL dose to placebo and its comparability to Foradil 12 mcg. Sensitivity analyses of the data from the pivotal trial as requested by the Agency in item 4 (c) and provided in this submission further substantiate these conclusions.
- Both DL-052 and DL-057 were dose-ranging studies that were not integrated with the pivotal study data and do not contribute to the overall finding of efficacy for formoterol fumarate inhalation solution.

Dey believes that sensitivity analyses for the dose ranging studies DL-052 and DL-057 will not yield any substantial information and will not have any impact on the conclusions reached to date. However, should the Agency decide that this information is essential, Dey agrees to provide the sensitivity analyses within approximately 2 weeks.

Based on the Agency's request to use the recently approved Brovana (arformoterol tartrate) labeling as a guide, Dey has also provided additional clarification and safety information in the package insert.

In Dey's response (A005, 18 October 2006) to the Agency's request for information dated 21 September 2006, the definition for the treatment assignment numerical codes (1=FFIS, 2=Foradil) for the TRT variable in the ae_d dataset was inadvertently not included in the define.pdf file submitted. Thus, this information is included in the revised define.pdf file submitted with this amendment.

25 January 2007
Badrul Chowdhury, MD, PhD, Division Director
Page 3

This information is being submitted electronically on 1 CD with a total file size of approximately 16 MB. In addition, the content of the index-md5.txt file is provided as an appendix as well as original signatures for the following documents:

- Cover Letter
- Form FDA 356h

The submission is virus free. All files have been scanned using McAfee VirusScan Enterprise, version 7.1.0. Please contact Marc Hefner at 707-224-3200 x2056 for electronic support.

If you have any questions, please do not hesitate to contact me at 707-224-3200 x4750.

Sincerely,



Michelle A. Carpenter, JD
Vice President, Regulatory and Clinical Affairs

Questions and Responses to Mid-Cycle Review Labeling and Clinical Comments in NDA 22-007 Letter Dated 13 December 2006

Responses to questions appear in indented form immediately following each Agency comment.

1. Because of safety concerns with use of long-acting beta agonists, we have determined that a Boxed Warning and Medication Guide will be required for this drug product. Submit revised labeling including a Boxed Warning and Medication Guide. Use the recently approved Brovana (arformoterol tartrate) labeling as a guide.

Response:

- Dey is submitting a revised Package Insert and annotated Package Insert that includes a Boxed Warning and corresponding Warnings and Precautions similar to that in the Brovana (arformoterol tartrate) package insert. Based on the Brovana approved Package Insert, additional clarification and safety information have also been included.
- Dey is submitting a Medication Guide and annotated Medication Guide similar to that of the Brovana (arformoterol tartrate) Medication Guide.
- Dey is submitting a revised SPL containing the revised Package Insert and Medication Guide

2. Submit a pharmacovigilance plan for formoterol fumarate inhalation solution (FFIS). At a minimum, the pharmacovigilance plan should include an evaluation of fatal and life-threatening respiratory adverse events in patients with COPD, safety in racial and ethnic subgroups, cardiovascular adverse events in patients with COPD, potential low frequency adverse events associated with use, and safety in populations other than patients with COPD, especially patients with asthma. As part of this plan, we request that you agree to conduct the following study:

- a. A multicenter, randomized, placebo-controlled, large, simple safety study to evaluate the effects of long term use of FFIS in patients with COPD.

CONFIDENTIAL

The objective of this trial would be to determine the risk of fatal and life-threatening respiratory events associated with the long term use of FFIS in patients with COPD. The study should be of adequate size and duration to meet the objective.

Response:

Dey is submitting a pharmacovigilance plan that includes a commitment to conduct the requested multicenter, randomized, placebo-controlled, large, simple safety study to evaluate the effects of long term use of FFIS in patients with COPD. Dey proposes to provide the Agency with a protocol for this study within 10 months of the approval date, to begin the study within 14 months of the approval date and to provide a final Clinical Study Report within 62 months of the approval date.

3. Because the formulation of FFIS is a solution for nebulization, use in urgent and emergency room settings as a treatment for acute bronchospasm in children with asthma is likely. Therefore, we request that you agree to conduct the following studies:

- a.) A safety and tolerability study with one or more doses and one or more dose levels of formoterol fumarate inhalation solution in children with asthma and/or obstructive airway disease. The objective would be to assess the safety and tolerability of formoterol fumarate inhalation solution in children 12 years of age and younger with asthma. Include a placebo or active control treatment group, as appropriate. Include children 12 years of age and younger so that the lower age limit would be based upon the age at which asthma/obstructive airway disease exists. The study should be of adequate size and duration to meet the objective.

Response:

As part of NDA 22-007 Dey submitted final study reports for 4 single dose, randomized, double-blind, double-dummy, active controlled, crossover dose-response studies that included 87 children 5 to 12 years of age with doses up to 12-times the proposed marketed dose of formoterol fumarate inhalation solution (Studies DL-048, DL-050,

CONFIDENTIAL

DL-053, DL-055) (Table 1). Final reports for these studies are provided in Module 5.3.5.4 of the original NDA 22-007.

Study DL-055 was a dose-ranging study that assessed safety and efficacy of 4 dose levels of formoterol fumarate inhalation solution (including the proposed dose of 20 mcg/2 mL) up to 12 hours post dose in 45 children with asthma ages 5 to 12 years. This study was recommended and agreed upon by the Agency at the End of Phase II meeting on 13 May 2003 (EOP II Minutes 13 May 2003; Fax 04 September 2003). Studies DL-053, DL-050 and DL-048 were dose-ranging studies that assessed safety and efficacy of 4 dose levels of formoterol fumarate inhalation solution above the proposed dose of 20 mcg/2 mL. These studies were conducted in a total of 42 children with asthma ages 5 to 11 years and 43 adolescent and adult patients with asthma ages 12 to 70 years.

The safety profile seen with formoterol fumarate inhalation solution in these studies with doses up to 12-times the proposed marketed dose was largely unremarkable and similar to the reference drug, Foradil[®] and placebo. Treatment emergent adverse events were similar across treatments, generally mild to moderate in nature, and resolved without sequelae. No serious adverse events were noted in any pediatric patients 12 years of age or under. All study medication doses were generally well tolerated. Minor dose dependent changes in heart rate and tremor were noted that did not require treatment and did not result in any patient being discontinued from the respective study.

Dey proposes that the pediatric data presented in the 4 studies with multiple dose-levels of formoterol fumarate inhalation solution up to 12 times the proposed marketed dose in asthma patients, fulfill the Agency's request to conduct a safety and tolerability study with one or more doses and one or more dose levels of formoterol fumarate inhalation solution in children with asthma and/or obstructive airway disease.

CONFIDENTIAL

Table 1: Studies in Children with Asthma

Study	Age	FFIS Dose*								Foradil*		PBO	Total
		2.5	5	10	20	40	80	162	244	12	24		
DL-055	5-12	43	43	44	44	-	-	-	-	44	-	45	45
DL-053	5-11	-	-	-	-	10	10	-	-	10	-	-	10
	12-70	-	-	-	-	11	11	-	-	10	-	-	11
DL-050	5-11	-	-	-	-	31	31	31	32	30	30	32	32
DL-048	12-70	-	-	-	-	31	29	29	30	30	31	29	32
Total		43	43	44	44	83	81	60	62	124	61	106	130

*dosage in mcg

- b. A safety and efficacy study with one or more doses and one or more dose levels of formoterol fumarate inhalation solution in children with asthma and/or obstructive airway disease presenting with an acute exacerbation. The objective would be to establish the safety and efficacy of formoterol fumarate inhalation solution in children 12 years of age and younger with an acute exacerbation of asthma. Include a placebo or active control treatment group, as appropriate. Include children 12 years of age and younger so that the lower age limit would be based upon the age at which asthma/obstructive airway disease exists. The study should be of adequate size and duration to meet the objective.

Response:

Dey agrees to conduct this study and would like to confirm that completion of this study qualifies NDA 22-007 for an additional six months of marketing exclusivity beyond the 180-days claimed according to 21 CFR 314.50(j) and 314.108(b)(4) and that it will

b(4)

4. Section 6.3.5 of the statistical analytical plan of trial 201-065 provides a formula for the calculation of standardized AUC of FEV1. It appears that this

CONFIDENTIAL

formula applies a proportional correction for time observed during the 12 hours after administration of trial medication. The AUC is standardized by the proportion of time observed within the 12 hour time window. This method typically will not provide a reasonable estimate of AUC when the proportion of time observed is small, due to the changing area under the curve of FEV1 with time after a bronchodilator is used.

- a. Describe the method of handling missing data within the 12-hour time period for trials 201-065, DL-052, and DL-057. Specifically, clarify if a proportional time correction for time observed was used in the calculation of FEV1 AUC in these trials.

Response:

Study 201-065 (Pivotal Safety and Efficacy Study)

The method of handling missing data within the 12-hour time period for study 201-065 was as described in Section 6.2 of the Statistical Analysis Plan (SAP) for the study as agreed and approved by the Agency (Pre-NDA Meeting Minutes). Specifically, a proportional time correction for time observed was used in the calculation of FEV1 (AUC) (L). For example, if the 9-hour timepoint was the last assessment for a patient at a visit, the Standardized Absolute FEV1 AUC (0-12) (L) (primary efficacy variable) value was calculated based upon the FEV1 assessments from time 0 to 9 hours and was standardized (divided) by 9. The last measured FEV1 measurement within the 12-hour time period was not carried forward to impute missing FEV1 measurements.

For patients with missing visits, the last observation carried forward (LOCF) method was used by carrying forward the last observed non-missing post-baseline standardized FEV1 AUC (0-12) (L) value.

Study DL-052 (Dose Ranging Study)

Missing FEV1 values for study DL-052 were imputed with pre-dose values as has been requested by the Agency. The primary efficacy variable, percent change in FEV1 AUC, was calculated by time-normalizing (dividing) by 12 (hours).

CONFIDENTIAL

Study DL-057 (Dose Ranging Study)

As specified in the statistical analysis plan for study DL-057, missing FEV1 values were assigned the last non-missing post-dose value (LOCF) after the 1-hour post-dose timepoint. The primary efficacy variable, FEV1 AUC (0-12), was calculated by time-normalizing (dividing) by 12 (hours).

- b. Provide the numbers of subjects with progressively missing hourly visits, per visit and treatment group (with percents of treatment groups), i.e. at 12 hours, at 9 and 12 hours, at 6, 9, and 12 hours, progressing down to entirely missing, for trials 201-065, DL-057 and DL-052 if applicable (see item (a)).

Response:

Study 201-065 (Pivotal Safety and Efficacy Study)

The Summary of Missing Data lists the number and percent of patients with progressively missing FEV1 data by treatment group at each visit and timepoint for study 201-065. Approximately 90% of the patients in the FFIS and Foradil groups, and approximately 80% of the patients in the placebo group completed all pulmonary function tests (5 min to 12 hour) for at least one post-baseline visit.

Approximately 14% of the patients in the FFIS and Foradil groups, and approximately 26% of the patients in the placebo group had a missing Week 12 standardized FEV1 AUC (0-12) (L) value. Therefore, the AUC data from a previous visit (LOCF) was used to impute the missing Week 12 standardized FEV1 AUC (0-12) (L) values.

Studies DL-052 and DL-057 (Dose-Ranging Studies)

Dey is requesting that the Agency reconsider its request for additional information in 4(b) for the dose-ranging studies DL-052 and DL-057 based on the following:

- Study DL-052 did not utilize the proposed marketed dose of FFIS 20 mcg/2 mL FFIS. The lowest dose in this trial, 40 mcg/2 mL, was twice that of the proposed marketed dose

CONFIDENTIAL

of FFIS. In addition, missing FEV1 data for study DL-052 was imputed with pre-dose values as has been requested by the Agency in 4(c) and FEV1 AUC values were not standardized by proportions of time less than 12 hours.

- Results from the original analyses of trial DL-057 that included 5 doses of formoterol fumarate (2.5 – 40 mcg) showed the FFIS 20 mcg dose was superior to placebo and comparable to Foradil 12 mcg. Based on this information, the Agency agreed that FFIS 20 mcg dose was appropriate for continued development in Phase III (End of Phase II Minutes 02 April 2004). The results from the pivotal trial 201-065 demonstrated the clinical and statistical superiority of FFIS 20 mcg/2 mL to placebo and comparability to Foradil 12 mcg. Sensitivity analyses of the data from the pivotal trial as requested by the Agency in item 4 (c) and provided in this submission further substantiate these conclusions.
- Both were dose-ranging studies that were not integrated with the pivotal study data and do not contribute to the overall finding of efficacy for FFIS.

Dey believes that sensitivity analyses for the dose ranging studies DL-052 and DL-057 will not yield any substantial information and will not have any impact on the conclusions reached to date. However, should the Agency decide that this information is essential, Dey agrees to provide the sensitivity analyses within approximately 2 weeks.

- c. In order to assess the impact of your standardization technique on the calculation of mean AUC, perform sensitivity analyses of the primary endpoints of trials 201-065, DL-057, and DL-052, if applicable, using various imputations of missing data for the subjects described in (b). We recommend that you include imputation of a subject's predose FEV1 for each missing FEV1 value that is not followed by an observed value.

CONFIDENTIAL

Response:

Study 201-065 (Pivotal Safety and Efficacy Study)

As requested by the Agency, Dey has conducted 4 different sensitivity analyses of the primary endpoint [FEV1 AUC (0-12) (L)] for study 201-065 (Table 2). All analyses, including imputation of a patient's predose FEV1 for each missing FEV1 value that is not followed by an observed value as recommended by the Agency, produced statistically significant results between FFIS and placebo ($p < 0.0022$).

In performing each of the sensitivity analyses two types of missing data were handled, missing FEV1 data within visits and missing visit AUC data. Missing FEV1 data within visits was imputed using three different imputation methods and subsequent FEV1 AUC (0-12) (L) values were derived. The values used for the 3 imputation methods were:

1) the patient's pre-dose FEV1 value, 2) the median FEV1 value of all available data for that visit/hour for all patients in all treatment groups and 3) the lowest (FFIS and Foradil) or highest (placebo) post-dose FEV1 value observed for that patient. The latter 2 imputations offer a more conservative approach by minimizing the difference between the active and placebo groups.

Missing visit FEV1 AUC (0-12) (L) data were completed using 2 different LOCF methods: 1) Last Observation Carried Forward (LOCF) of FEV1 AUC (0-12) values and 2) patient's lowest (FFIS and Foradil) or highest (placebo) FEV1 AUC (0-12) (L) value.

The results from these analyses support the primary efficacy outcome of the initial analysis conducted according to the Statistical Analysis Plan that FFIS 20 mcg/2 mL administered twice daily provided significant ($p < 0.0001$) improvement in respiratory status compared to placebo and confirm that the data from this study are robust.

CONFIDENTIAL

Table 2: 201-065 Sensitivity Analyses

Sensitivity Analysis	Imputation Method (missing data within visit)	LOCF Method (missing visit)	Tables	p-value
SAP	None (time adjusted)	LOCF (AUC value)	14.2.1.1.1	<0.0001
			14.2.1.2.1.1	
			14.2.1.2.2.1	
1	Pre-dose FEV1 value (as requested by the FDA)	LOCF (AUC value)	A.1.1.1	<0.0001
			A.1.2.1	
			A.1.3.1	
2	Pre-dose FEV1 value (as requested by the FDA)	Highest AUC value for Placebo, lowest post-dose AUC value for active	A.1.1.2	<0.0001
			A.1.2.2	
			A.1.3.2	
3	Median FEV1 value at timepoint, across all patients	Highest AUC value for Placebo, lowest post-dose AUC value for active	A.2.1.2	0.0022
			A.2.2.2	
			A.2.3.2	
4	Best FEV1 value for Placebo, worst post-dose FEV1 value for active	Highest AUC value for Placebo, lowest post-dose AUC value for active	A.3.1.2	<0.0001
			A.3.2.2	
			A.3.3.2	

Studies DL-052 and DL-057 (Dose-Ranging Studies)

Dey is requesting that the Agency reconsider its request for additional information in 4(c) for the dose-ranging studies DL-052 and DL-057 based on the following:

- Study DL-052 did not utilize the proposed marketed dose of FFIS 20 mcg/2 mL. The lowest dose in this study, 40 mcg/2 mL, was twice that of the proposed marketed dose of FFIS. In addition, missing FEV1 data for study DL-052 was imputed with pre-dose values as requested by the Agency in 4(c) and FEV1 (AUC) (L) values were not standardized by proportions of time less than 12 hours.
- Results from the original analyses of trial DL-057 that included 5 doses of formoterol fumarate (2.5 – 40 mcg) showed the FFIS 20 mcg dose was superior to placebo and comparable to Foradil 12 mcg. Based on this information, the Agency agreed that FFIS 20 mcg dose was appropriate

CONFIDENTIAL

for continued development in Phase III (End of Phase II Minutes 02 April 2004). The results from the pivotal trial 201-065 demonstrated the clinical and statistical superiority of FFIS 20 mcg/2 mL to placebo and comparability to Foradil 12 mcg. Sensitivity analyses of the data from the pivotal trial as requested by the Agency in item 4 (c) and provided in this submission further substantiate these conclusions.

- Both were dose-ranging studies that were not integrated with the pivotal study data and do not contribute to the overall finding of efficacy for FFIS.

Dey believes that sensitivity analyses for the dose ranging studies DL-052 and DL-057 will not yield any substantial information and will not have any impact on the conclusions reached to date. However, should the Agency decide that this information is essential, Dey agrees to provide the sensitivity analyses within approximately 2 weeks.

5. Your NDA does not contain a summary of pulmonary function testing in the subjects enrolled in the open-label period of trial DL-059. Submit a by-treatment summary, with data sets or listings, of spirometry data for enrolled subjects at the onset (or at the closest visit available) of the open-label period of trial DL-059.

Response: As a result of the randomization error that occurred in the double-blind portion of study DL-059 which resulted in patients receiving inconsistent medications throughout the 12-week period, the Agency agreed that efficacy data from this study would not be presented in the NDA (Pre-NDA Meeting Minutes), thus spirometry data was not included. In response to the Agency's request, Dey is providing a Summary of Pulmonary Function Tests and a derived dataset (spiro_d.xpt) as well as a revised version of the data definition tables (define.pdf) for all datasets. The dataset that contains all spirometry data collected during the double-blind period for patients that continued into the open-label phase is provided with this amendment (1=FFIS, 2=Foradil). The Summary of Pulmonary Function Tests summarizes the

CONFIDENTIAL

open-label baseline spirometry data for these patients, which is defined as the last available double-blind observation where the patient had both FEV1 and FVC values.

APPEARS THIS WAY ON ORIGINAL

CONFIDENTIAL

**Formoterol Fumarate Inhalation Solution 20 mcg/2 mL
NDA 22-007
Pharmacovigilance Plan**

To assess the safety of Formoterol Fumarate Inhalation Solution 20 mcg/2 mL (FFIS), Dey intends to monitor post-marketing SAEs and to provide 6 month and 12 month post-entry-to-market updates on these to the FDA. These updates will include an evaluation of fatal and life-threatening respiratory adverse events in patients with COPD, serious cardiovascular adverse events in patients with COPD, any potential low frequency adverse events associated with use of FFIS that are rare yet serious, and safety in populations other than patients with COPD, especially patients with asthma. These reports will include subgroup analyses by race and ethnicity.

All SAE reports of fatal and life-threatening respiratory adverse events or fatal and life-threatening cardiovascular adverse events reported to Dey will follow a pre-formatted SAE report form designed to capture important information in a uniform way on each subject for these particular adverse events. It is hoped that this will result in an enhanced quality of SAE reports. A copy of this form will be submitted to the Agency for review and input.

As part of this plan, Dey will conduct a multicenter, randomized, placebo-controlled, large, simple safety study to evaluate the effects of long term use of FFIS in patients with COPD. The objective of this trial will be to determine the risk of fatal and life-threatening respiratory events associated with the long term use of FFIS in patients with COPD. The study will be of adequate size and duration to meet the objective.

b(4)

CONFIDENTIAL



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

Memorandum of Facsimile Correspondence

Date: December 13, 2006

To: Michelle A. Carpenter
V.P., Regulatory Affairs and Clinical Development

Fax: (707) 224-1364

Phone: (707) 224-3200 x4750

From: Akilah Green, RN, MS
Senior Regulatory Management Officer
Division of Pulmonary and Allergy Products

Subject: NDA 22-007

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) 796-2300 and return it to us at FDA, 10903 New Hampshire Ave, Building 22, DPAP, Silver Spring, MD 20993.

Thank you.

We are reviewing your submission dated June 28, 2006, and we have the following comments and requests for information:

1. Because of safety concerns with use of long-acting beta agonists, we have determined that a Boxed Warning and Medication Guide will be required for this drug product. Submit revised labeling including a Boxed Warning and Medication Guide. Use the recently approved Brovana (arformoterol tartrate) labeling as a guide.
2. Submit a pharmacovigilance plan for formoterol fumarate inhalation solution (FFIS). At a minimum, the pharmacovigilance plan should include an evaluation of fatal and life-threatening respiratory adverse events in patients with COPD, safety in racial and ethnic subgroups, cardiovascular adverse events in patients with COPD, potential low frequency adverse events associated with use, and safety in populations other than patients with COPD, especially patients with asthma. As part of this plan, we request that you agree to conduct the following study:
 - a. A multicenter, randomized, placebo-controlled, large, simple safety study to evaluate the effects of long term use of formoterol fumarate inhalation solution in patients with COPD. The objective of this trial would be to determine the risk of fatal and life-threatening respiratory events associated with the long term use of formoterol fumarate inhalation solution in patients with COPD. The study should be of adequate size and duration to meet the objective.
3. Because the formulation of FFIS is a solution for nebulizations, use in urgent and emergency room settings as a treatment for acute bronchospasm in children with asthma is likely. Therefore, we request that you agree to conduct the following studies:
 - a. A safety and tolerability study with one or more doses and one or more dose levels of formoterol fumarate inhalation solution in children with asthma and/or obstructive airway disease. The objective would be to assess the safety and tolerability of formoterol fumarate inhalation solution children 12 years of age and younger with asthma. Include a placebo or active control treatment group, as appropriate. Include children 12 years of age and younger so that the lower age limit would be based upon the age at which asthma/obstructive airway disease exists. The study should be of adequate size and duration to meet the objective.
 - b. A safety and efficacy study with one or more doses and one or more dose levels of formoterol fumarate inhalation solution in children with asthma and/or obstructive airway disease presenting with an acute exacerbation.

The objective would be to establish the safety and efficacy of formoterol fumarate inhalation solution in children 12 years of age and younger with an acute exacerbation of asthma. Include a placebo or active control treatment group, as appropriate. Include children 12 years of age and younger so that the lower age limit would be based upon the age at which asthma/obstructive airway disease exists. The study should be of adequate size and duration to meet the objective.

4. Section 6.3.5 of the statistical analytical plan of trial 201-065 provides a formula for the calculation of standardized AUC of FEV₁. It appears that this formula applies a proportional correction for time observed during the 12 hours after administration of trial medication. The AUC is standardized by the proportion of time observed within the 12 hour time window. This method typically will not provide a reasonable estimate of AUC when the proportion of time observed is small, due to the changing area under the curve of FEV₁ with time after a bronchodilator is used.
 - a. Describe the method of handling missing data within the 12-hour time period for trials 201-065, DL-052, and DL-057. Specifically, clarify if a proportional time correction for time observed was used in the calculation of FEV₁ AUC in these trials.
 - b. Provide the numbers of subjects with progressively missing hourly visits, per visit and treatment group (with percents of treatment group), i.e. at 12 hours, at 9 and 12 hours, at 6, 9, and 12 hours, progressing down to entirely missing, for trials 201-065, DL-057 and DL-052 if applicable (see item (a)).
 - c. In order to assess the impact of your standardization technique on the calculation of mean AUC, perform sensitivity analyses of the primary endpoints of trials 201-065, DL-057, and DL-052, if applicable, using various imputations of missing data for the subjects described in (b). We recommend that you include imputation of a subject's predose FEV₁ for each missing FEV₁ value that is not followed by an observed value.
5. Your NDA does not contain a summary of pulmonary function testing in the subjects enrolled in the open-label period of trial DL-059. Submit a by-treatment summary, with data sets or listings, of spirometry data for enrolled subjects at the onset (or at the closest visit available) of the open-label period of trial DL-059.

If you have any questions, you may contact Ms. Akilah Green, Senior Regulatory Management Officer, at 301-796-1219.

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

/s/

Akilah Green
12/13/2006 12:09:33 PM
CSO

MEMORANDUM**Division of Medication Errors and Technical Support
Office of Surveillance and Epidemiology
WO 22, Mailstop 4447, HFD-420
Center for Drug Evaluation and Research**

To: Badrul Chowdhury, MD
Director, Division of Pulmonary and Allergy Products, HFD-570

Through: Alina Mahmud, RPh, MS, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

From: Kimberly Pedersen, RPh, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

Date: November 11, 2006

Subject: OSE Review 2006-137
Formoterol Fumarate Inhalation Solution
NDA 22-007

This memorandum is in response to an August 29, 2006 request from your Division for a review of the revised labeling for Formoterol Fumarate Inhalation Solution. DMETS previously reviewed two proposed proprietary names and associated labels and labeling for this drug product in October 2005 (OSE # 05-0244, 05-0244-1). At that time, DMETS did not recommend the use of the proprietary names " — " and " — " and recommended labeling/packaging changes. The sponsor has subsequently submitted three additional names for review (Performist, — and —), which are currently under review by DMETS. The review of the proprietary names will be forwarded to the Division in a separate memorandum. The sponsor submitted insert labeling (including patient information leaflet and patient package insert), carton labeling, foil container label, and individual vial embossing for review and comment in this review. b(4)

A. GENERAL COMMENTS

1. DMETS notes that the proposed labeling does not include the black box warning as found in the Foradil and Symbicort labeling. Revise to include this warning.
2. Revise the presentation of dosing frequency from "twice daily" to " — " to reduce confusion. b(4)

B. INSERT LABELING (Package Insert)**1. DOSAGE AND ADMINISTRATION**

See General Comments A-2.

2. HOW SUPPLIED/STORAGE AND HANDLING

- a. For clarity and as practitioners commonly reference this section, include information on the 3 month expiration statement after dispensing as shown on the carton labeling to aid in the proper storage and usage.
- b. As noted in our previous review, DMETS continues to recommend an inclusion of the established name with the first occurrence of the proprietary name in this section.

3. PATIENT COUNSELING INFORMATION SECTION

As noted in our previous review, DMETS continues to recommend the following statements be included: "Do not take by mouth" and "Throw plastic dispensing container away immediately after use. The container and top, due to their small size, pose a danger of choking to young children."

C. PATIENT PACKAGE INSERT

1. "What is TRADE NAME 20 mcg/2 mL?" Section

Revise the first sentence to read "TRADE NAME 20 mcg/2 mL is a medicine that is used every _____" from the original "_____ statement to limit the potential for dosing frequency confusion. **b(4)**

2. "How should I use TRADE NAME 20 mcg/2 mL?" Section

Consider the addition of a statement that communicates that the patient should not use long-acting beta agonists concurrently with TRADE NAME.

3. "How should I store TRADE NAME 20 mcg/2 mL?" Section

Reference is made to bullet 4. In lieu of the _____ statement, revise the statement so that the patient understands the product is to be used within 3 months of the dispensing date or by the product expiration date, which ever comes first. **b(4)**

D. CARTON LABELING

1. Assure the established name is at least ½ the size of the proprietary name pursuant to 21 CFR 201(g) (2).
2. Increase the prominence of the product strength as it is currently overshadowed by the Trade Name and "2 mL" statement. This strength (20 mcg) is of great importance as the currently marketed Foradil contains 12 mcg of formoterol.
3. Delete the _____ Currently this presentation is larger than the product strength. Additionally, it is duplicative since the volume is presented in conjunction with the strength. **b(4)**
4. Revise the "Dispense Date:" and "Use by" box. As currently presented, there is no space for the entry of a dispensing date. Furthermore, the "Use by" box is referenced throughout the labeling. Thus, consider the deletion of the "Dispense date:" statement since it is not relevant. The previous sentence (Discard three months after dispense date) describes the use by date.

E. CONTAINER (INHALATION VIAL TEXT EMBOSSING)

The picture of the individual vial illustrates embossing on both sides, which has been found to result in illegibility of the text in post-marketing reporting. Therefore, DMETS recommends the sponsor emboss the established name and strength on one side of the body of the vial to help patients and practitioners identify the vial content. These data are currently embossed on the tab of the vial. The tab space can then include the tradename, route of administration, lot, and expiration.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-796-0080.

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

/s/

Alina Mahmud
12/21/2006 11:09:48 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
12/21/2006 02:00:46 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
12/21/2006 02:15:44 PM
DRUG SAFETY OFFICE REVIEWER



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

Date: November 3, 2006

To: Michelle A. Carpenter V.P., Regulatory Affairs and Clinical Development	From: Akilah Green, RN, MS Senior Regulatory Management Officer
Company: Dey, L.P.	Division of Pulmonary and Allergy Products
Fax number: 707-224-1364	Fax number: 301-796-9718
Phone number: 707-224-3200 X4750	Phone number: 301-796-1219

Subject: NDA 22-007 Meeting Request Granted Letter

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES NO

**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, or a person authorized to deliver this document to 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 have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-007

Dey, L. P.

Attention: Michelle J. Carpenter
Vice President, Regulatory and Clinical Affairs

Dear Ms. Carpenter:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Foradil (formoterol fumarate) Inhalation Powder.

We also refer to your October 19, 2006, correspondence, received October 20, 2006, requesting a meeting to discuss the acceptability of the development of a modified Aerolizer-type inhaler (Concept 1) to support registration of Foradil in this inhaler for patients with _____ COPD. **b(4)**

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: November 20, 2006
Time: 12:00-1:00 PM
Phone Arrangements: TBD by Dey, L.P.

CDER participants: Laurie Burke, Office of New Drugs, Immediate Office,
Study Endpoints and Labeling Development Team
Jeanie Delasko, Office of New Drugs, Immediate Office,
Study Endpoints and Labeling Development Team
Akilah Green, RN, MS, Senior Regulatory Management
Officer

If you have any questions, call Akilah Green, Senior Regulatory Management Officer, at (301) 796-1219.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Supervisory CSO
Division of Pulmonary Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Colette Jackson
11/3/2006 01:53:01 PM
Signed for S. Barnes.



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

Date: September 21 , 2006

To: Michelle A. Carpenter V.P., Regulatory Affairs and Clinical Development	From: Akilah Green, RN, MS Senior Regulatory Management Officer
Company: Dey, L.P.	Division of Pulmonary and Allergy Products
Fax number: 707-224-1364	Fax number: 301-796-9718
Phone number: 707-224-3200 X4750	Phone number: 301-796-1219

Subject: NDA 22-007

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES NO

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, or a person authorized to deliver this document to 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 have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 22-007

Formoterol Fumarate Inhalation Solution

Your submission dated June 28, 2006, is currently under review, and we have the following comments and requests for information regarding the open label portion of Study 059 for the AE data file (AE_D):

1. Add a variable (column) representing the scheduled treatments. The treatment this variable would represent would be based on the original randomization schedule rather than the treatment the patient first received at the beginning of the double blind period.
2. The definition of the variable TRT takes numerical values 1 and 2 without explanation. Clarify the treatment assignment encoded by values 1 and 2.
3. A number of variables carried user-defined SAS formats, but neither the SAS format catalog nor the SAS procedure that created those formats was submitted. Submit the SAS format catalog and/or the SAS PROC FORMAT programs to enable decoding of the variables in AE_D.

If you have any questions, you may contact Ms. Akilah Green, Senior Regulatory Management Officer, at 301-796-1219.

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

/s/

Akilah Green

9/21/2006 09:13:51 AM

CSO

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-007 Supplement # Efficacy Supplement Type SE-

Proprietary Name:
Established Name: Formoterol Fumarate
Strengths: 20 mcg/2 mL

Applicant: Dey, L.P.
Agent for Applicant (if applicable):

Date of Application: June 28, 2006
Date of Receipt: June 29, 2006
Date clock started after UN:
Date of Filing Meeting: August 22, 2006
Filing Date: August 28, 2006
Action Goal Date (optional): February 28, 2006 User Fee Goal Date: April 29, 2007

Indication(s) requested: **Long-term, twice daily (morning and evening) administration in the maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema.**

Type of Original NDA: (b)(1) (b)(2) X
AND (if applicable)
Type of Supplement: (b)(1) (b)(2)

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S X P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) 5
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES X NO

User Fee Status: Paid X Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application.

Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES NO X
If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES NO X
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO X
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES NO
- Does the submission contain an accurate comprehensive index? YES X NO
If no, explain:
- Was form 356h included with an authorized signature? YES X NO
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES X NO
If no, explain: *Missing patent certification information and did not list the patent number of the RLD. Information requested from Dey and submitted on July 24, 2006.*

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES NO X
2. This application is an eNDA or combined paper + eNDA YES NO X
This application is: All electronic Combined paper + eNDA
This application is in: NDA format CTD format
Combined NDA and CTD formats

Does the eNDA, follow the guidance?
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>) YES NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES X

If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES X NO
- Exclusivity requested? YES X 3Years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES X NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge"

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES X NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES X NO
- Is this submission a partial or complete response to a pediatric Written Request? YES NO X

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES X NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section) YES X NO
- PDUFA and Action Goal dates correct in tracking system? YES X NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: **64,525, and 68,782**
- Are the trade, established/proper, and applicant names correct in COMIS? YES X NO
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) April 2, 2004 NO
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) September 20, 2005 NO
If yes, distribute minutes before filing meeting.
- Any SPA agreements? Date(s) _____ NO X
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES X NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES X NO

If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES X NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES X NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? N/A YES X NO
- Risk Management Plan consulted to OSE/IO? N/A X YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA X YES NO

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES X NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to EA officer, OPS? YES NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 22, 2006

NDA #: 22-007

DRUG NAMES: Formoterol Fumarate Inhalation Solution

APPLICANT: Dey, L.P.

BACKGROUND: This is a 505(b)(2) NDA for COPD. The reference listed drugs for this application are NDA 20-831 and NDA 21-279, Foradil Aerolizer Inhalation Powder. This application provides for a change in dosage form from inhalation powder to inhalation solution.

(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Akilah Green, Badrul Chowdhury, Peter Starke, James Kaiser, Timothy Robison, C. Joe Sun, Prasad Peri, Emmanuel Fadiran, Partha Roy, Ruthanna Davi, Ted Guo, Robert Boucher, Sally Limb, Miranda Raggio, Carol Hill

ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline/Organization</u>	<u>Reviewer</u>
Medical:	James Kaiser, M.D.
Secondary Medical:	Peter Starke, M.D.
Statistical:	Ted Guo, Ph.D.
Pharmacology:	Timothy Robison, Ph.D.
Statistical Pharmacology:	
Chemistry:	John Hill, Ph.D.
Environmental Assessment (if needed):	
Biopharmaceutical:	Partha Roy, Ph.D.
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	Tejashri Purohit-Sheth, M.D.
OPS:	
Regulatory Project Management:	Akilah Green, M.S., R.N.
Other Consults:	

Per reviewers, are all parts in English or English translation? YES NO
If no, explain:

CLINICAL FILE REFUSE TO FILE

- Clinical site audit(s) needed? YES NO
If no, explain:

- Advisory Committee Meeting needed? YES, date if known _____ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
N/A YES NO

CLINICAL MICROBIOLOGY N/A FILE REFUSE TO FILE

STATISTICS N/A FILE REFUSE TO FILE

BIOPHARMACEUTICS FILE REFUSE TO FILE

- Biopharm. study site audits(s) needed? YES NO

PHARMACOLOGY/TOX N/A FILE REFUSE TO FILE

- GLP audit needed? YES NO

CHEMISTRY FILE REFUSE TO FILE

- Establishment(s) ready for inspection? YES NO
- Sterile product? YES NO
- If yes, was microbiology consulted for validation of sterilization? YES NO

ELECTRONIC SUBMISSION:

Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
 - No filing issues have been identified.
 - Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

- 4. X If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
- 5. X Convey document filing issues/no filing issues to applicant by Day 74.

Akilah Green, M.S., R.N.
Regulatory Project Manager

**APPEARS THIS WAY
ON ORIGINAL**

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): **NDA 20-831 Foradil Aerolizer and NDA 21-279 Foradil Aerolizer**

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.) YES NO

If "Yes," skip to question 7.

4. Is this application for a recombinant or biologically-derived product? YES NO

If "Yes" contact your ODE's Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," to (a) skip to question 6. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO

If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES X NO

(*Pharmaceutical alternatives* are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," to (a) skip to question 7. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES X NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES X NO

If "Yes," to (c), proceed to question 7.

NOTE: If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.

If "No," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s): **Foradil Aerolizer (formoterol fumarate) Inhalation Powder**

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES NO X

If "No," skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). **This application provides for a change in dosage form, from inhalation powder to inhalation solution.**

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES NO X

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES NO X

11. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9). YES NO X
12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES X NO
13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

Not applicable (e.g., solely based on published literature. See question # 7

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

X 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s): 6,488,027

NOTE: IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug. **The pivotal study, 201-065, is based on the studies conducted for the approval of Foradil Aerolizer.**

YES X NO

If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug.

Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES X NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A YES X NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES NO X

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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

/s/

Akilah Green
9/14/2006 11:57:19 AM
CSO



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

Date: September 11, 2006

To: Michelle A. Carpenter V.P., Regulatory Affairs and Clinical Development	From: Akilah Green, RN, MS Senior Regulatory Management Officer
Company: Dey, L.P.	Division of Pulmonary and Allergy Products
Fax number: 707-224-1364	Fax number: 301-796-9718
Phone number: 707-224-3200 X4750	Phone number: 301-796-1219
Subject: NDA 22-007 Filing Letter	

Total no. of pages including cover: 5

Comments:

Document to be mailed: YES NO

**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, or a person authorized to deliver this document to 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 have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-007

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

Attention: Michelle A. Carpenter, JD
Vice President, Regulatory and Clinical Affairs

Dear Ms. Carpenter:

Please refer to your June 28, 2006, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Formoterol Fumarate Inhalation Solution.

We also refer to your submission dated July 24, 2006.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on August 28, 2006, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

1. Foradil Aerolizer currently includes a boxed warning and medication guide for use in patients with asthma (labeling approved June 16, 2006). The need for a boxed warning and medication guide for formoterol fumarate inhalation solution (FFIS) will be a review issue.
2. Although studies have been conducted suggesting that long-acting beta agonists may increase the risk of asthma-related death, corresponding safety studies have not been performed in COPD patients. The need for obtaining safety information in COPD patients, such as a large simple safety study, will be a review issue.
3. Because of the configuration of FFIS as a solution for nebulization, use in urgent and emergency room settings as a treatment for acute bronchospasm is likely. While we recognize your commitment to a risk management plan to minimize use in patients with asthma, the need for obtaining safety information for treatment for acute bronchospasm will be a review issue.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of

13. You have submitted a Patient Package Insert with your application. Therefore, the patient counseling information statement must state: **See 17 for PATIENT COUNSELING INFORMATION – and FDA approved patient labeling.**
[See 21 CFR 201.57(a)(14)]
14. A revision date must be placed at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, the date will be determined by the month/year of approval.
15. When the labeling is in final draft, the Highlights must be limited in length to one half page, in 8 point type. [See 21 CFR 201.57(d)(8)]
16. A horizontal line must separate the Highlights, Contents, and Full Prescribing Information. [See 21 CFR 201.57(d)(2)]
17. Submit the completed Structured Product Labeling (SPL) Highlights Data Elements Table. To complete the Highlights Data Elements Table, refer to the following two documents at the FDA Data Standards Council website (<http://www.fda.gov/oc/datacouncil>) under SPL: “Companion Document for SPL Release 2 Implementation Guide for Highlights DRAFT” and “SPL Highlights Data Element Table.” This table must be filled out with the terms that have been proposed for the Highlights data elements. The companion document provides information on the terminology to be used. If you need assistance completing the Highlights data elements portion of your application, contact spl@fda.hhs.gov.

Full Prescribing Information: Contents:

18. The Agency recommends the use of a two-column format for the Full Prescribing Information: Contents. [Implementation Guidance]

Full Prescribing Information (FPI):

19. Regarding Drug Abuse and Dependence, is this information necessary? If clearly inapplicable, you can omit. [See 21 CFR 201.56(d)(4)]
20. The manufacturer information should be located after the Patient Counseling Information section, at the end of labeling. [Best Practices]

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

NDA 22-007

Page 4

If you have any questions, call Ms. Akilah Green, Senior Regulatory Management Officer, at (301) 796-1219.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Badrul Chowdhury
9/11/2006 04:13:25 PM

This application contains the following items: (Check all that apply)	
<input type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input checked="" type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input type="checkbox"/>	20. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT <i>Michelle A. Carpenter</i>	TYPED NAME AND TITLE Michelle A. Carpenter, JD Vice President, Regulatory & Clinical Affairs	DATE: 06 September 2006
ADDRESS (Street, City, State, and ZIP Code) 2751 Napa Valley Corporate Drive, Napa, CA 94558		Telephone Number (707) 224-3200 x4750

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Regulatory Document Room
1-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.



28 June 2006

Food and Drug Administration
Center for Drug Evaluation and Research
Badrul Chowdhury, MD, PhD, Division Director
Division of Pulmonary and Allergy Drug Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: New Drug Application No. 22-007
Product: Formoterol Fumarate Inhalation Solution, 20 mcg/2 mL
Indication: Chronic Obstructive Pulmonary Disease

Dear Dr. Chowdhury,

Pursuant to §505(b)(2) of the Federal Food, Drug and Cosmetic Act and in accordance with Title 21 of the Code of Federal Regulations, §314.50, Dey, LP (Dey) herewith submits New Drug Application (NDA) 22-007 for Formoterol Fumarate Inhalation Solution 20 mcg/2 mL (FFIS) for the long-term, twice daily administration in the maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema. Previous information concerning this product for COPD has been submitted to the Agency under Investigational New Drug Application (IND) 68,782, filed on 15 December 2003.

As agreed with the Agency, the primary clinical support of this NDA for COPD, includes five (5) clinical studies under IND 68,782 with FFIS in COPD patients. These studies include one Phase I pharmacokinetic study (DL-056), two Phase II dose-ranging studies (DL-052 and DL-057), one Phase III 12-Week Safety and Efficacy study (201-065) and one Phase III Long-Term (1 year) Safety Study (DL-059 Open Label). All clinical studies in support of the safety and efficacy of FFIS were designed in collaboration and agreement with the Agency, including selection of 20 mcg/2 mL as the appropriate dose. In addition, the pivotal study, 201-065, is based on the studies conducted for the approval of Foradil[®] Aerolizer[®], the reference drug for this 505(b)(2) NDA.

All clinical studies performed in support of this NDA were conducted in compliance with the requirements set forth in 21 CFR Parts 50 and 56, International Conference on Harmonisation (ICH E6) guidelines; and standard operating procedures (SOPs) for

28 June 2006
Badrul Chowdhury, MD, PhD, Division Director
Page 2

clinical investigation and documentation in force at the time the studies were conducted and analyzed.

All nonclinical studies performed in support of this NDA were conducted in compliance with the requirements set forth in 21 CFR, Part 58 Good Laboratory Practices for Nonclinical Laboratory Studies and standard operating procedures (SOPs) for nonclinical investigation and documentation in force at the time the studies were conducted and analyzed.

The methods used in, and the facilities and controls used for, the manufacture, processing, packing, and holding of the drug substance or drug product are in compliance with the Current Good Manufacturing Practice regulations set forth in 21 CFR, Parts 210 and 211.

Dey has been in contact with the Office of Information Management (Electronic Regulatory Submissions and Review) within CDER to confer on the technical requirements and organization of the electronic common technical document (eCTD) format. The initial pilot eCTD (Sample Submission No. 900099) was submitted on 24 June 2005. On 28 September 2005, Sample Submission No. 900099 was approved and Dey was given permission to send a "live" eCTD application to CDER.

This application is being submitted entirely electronically on 1 DVD with a total file size of approximately 2 GB. In addition, original signatures are provided in hard copy for the following documents:

- Cover letter
- Form FDA 356h, Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use
- Form FDA 3397 (the applicable User Fee of \$767,400 was wire transferred on 5/3/06 under the User Fee ID number of PD3006513 and received by the Agency on 5/5/06)
- Debarment Certification

28 June 2006

Badrul Chowdhury, MD, PhD, Division Director

Page 3

- Financial Certification (FDA Form 3454): Financial Interests and Arrangements of Clinical Investigators
- Financial Disclosures (FDA Form 3455)
- Patent Certifications (two) (FDA Form 3542a)
- Contents of the index-md5.txt file

The submission is virus free. All files have been scanned using McAfee VirusScan Enterprise, version 7.1.0. Please contact Marc Hefner at 707-224-3200 x2056 for electronic support.

All facilities involved in the manufacture and release of the drug product are ready for preapproval inspection (PAI) as of this date, 28 June 2006.

If you have any questions, please do not hesitate to contact me at 707-224-3200 x4750 or 707-396-0039 (cell).

Sincerely,



Michelle A. Carpenter, JD
Vice President, Regulatory and Clinical Affairs

DIVISION DIRECTOR'S MEMORANDUM

Date: April 27, 2007

To: NDA 22-007

From: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary and Allergy products, CDER, FDA

Product: Perforomist (formoterol fumarate) Inhalation Solution

Applicant: Dey, LP

Administrative and Introduction

Dey submitted a 505(b)(2) new drug application (NDA 22-007) on June 28, 2006, (received on June 29, 2006, CDER stamp date), for use of Perforomist (formoterol fumarate) Inhalation Solution for the maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. The proposed dose is 20 mcg administered twice a day by nebulization. The PDUFA due date for this application is April 29, 2007. This application references Foradil Aerolizer (formoterol fumarate inhalation powder) (NDAs 21-279 and 20-831, Novartis) in support of the 505(b)(2) regulatory pathway. Foradil Aerolizer is currently approved for maintenance treatment of asthma and in the prevention of bronchospasm in patients 5 years of age and older, and for maintenance treatment of bronchoconstriction in patients with COPD including chronic bronchitis and emphysema. Note that Dey is only seeking approval in COPD patients. Dey's stated reason for not seeking

Dey has submitted the necessary CMC data, pre-clinical data, and clinical data that support approval of this application. However, the application contains a certification pursuant to section 505(b)(2)(A)(iv) (a "Paragraph IV certification") to U.S. Patent No. 6,488,027, which expires on March 8, 2019. Dey submitted Paragraph IV certification to their application on March 12, 2007. The patent owner and NDA holder received notice of the certification on March 15, 2007. If the patent owner or NDA holder disagrees with Dey's assertion that the patent is invalid, unenforceable, or not infringed and files a patent infringement lawsuit within 45 days of receipt of Dey's notice (i.e., by April 30, 2007), there will be a 30 month stay on approval of the application, which will have begun on March 15, 2007. Because that 45 day period has not yet expired, the application may only be tentatively approved.

Chemistry, Manufacturing, and Controls, and Establishment Evaluation

The drug substance formoterol fumarate dihydrate is not a new molecular entity; it is present in the currently approved product Foradil Aerolizer. The formulation is a sterile

b(4)

isotonic aqueous solution of formoterol fumarate in saline with pH adjusted to 5.0 with citric acid and sodium citrate. The final drug product is a 2-mL solution containing 20 mcg of formoterol fumarate contained in 2.5-mL low-density polyethylene (LDPE) unit-dose vials that are over wrapped individually in ~~_____~~ fowl pouches. A carton contains 60 unit-dose individually pouched vials.

b(4)

All DMFs associated with this application are acceptable. The drug substance is manufactured by either ~~_____~~, or Merck Development Center Private Limited in India. The formulation and the final drug product are manufactured by Dey in Napa, California. All manufacturing and testing facilities associated with this drug product have acceptable EER status.

There were several CMC issues identified by the CMC review team early in the review period. Those were communicated to Dey in a discipline review letter. Dey resolved these issues and the CMC team recommends an approval action. I concur with that recommendation.

Pharmacology and Toxicology

Dey did not conduct a comprehensive pharmacology and toxicology program for this application, and relies on the Foradil Aerolizer application. Dey conducted a 14-day inhalation toxicology study with rats to bridge the inhalation solution formulation for nebulization and the dry powder formulation in Foradil Aerolizer. Dr. Robison performed the Pharmacology and Toxicology review of this application and recommends an approval action. I concur with that recommendation.

Clinical Pharmacology and Biopharmaceutics

Dey submitted results from one pharmacokinetic (PK) study (Study DL-056) with this application. This study compares systemic exposure between Perforomist and Foradil Aerolizer. The OCP team reviewed the study and has determined that this study is adequate and recommends an approval action. I concur with that recommendation. Brief comments on some key findings from this study are made in the following paragraph.

Study DL-056 was single-dose, randomized, 4-way crossover in design conducted in one center in the United States, in 13 COPD patients. The study compared the PK of Perforomist 10 mcg, 20 mcg, and 244 mcg, all delivered by Pari LC Plus nebulizer and Foradil Aerolizer 12 mcg. Plasma and urine formoterol concentrations were assessed using a LC/MS method with a lower limit of quantification (LLOQ) of 2.5 pg/mL. Following analysis it was apparent that the assay method was not sensitive enough for plasma PK profiling because majority of the plasma samples had formoterol levels near or below the LLOQ. However, the urinary formoterol excretion data were informative. The amount of formoterol excreted in urine with the three Perforomist dose showed linear kinetics, and the amount of formoterol excreted following Perforomist 20 mcg dose was 14% lower compared to the Foradil Aerolizer 12 mcg dose. The urinary data along with the limited plasma PK data support the conclusion that formoterol systemic

exposure after administration of Perforomist 20 mcg is comparable or possibly lower than Foradil Aerolizer 12 mcg.

Clinical and Statistical

Overview of the clinical program:

The clinical program for Perforomist was relatively small but appropriate given that the proposed indication is limited to COPD only and that the drug in a different formulation is already approved for the same indication. The pivotal clinical studies included two dose-ranging studies (studies DL-052, and DL-057), one 12-week confirmatory efficacy and safety study (study DL-201-065), and one one-year safety study (study DL-059). Detailed review of these studies can be found in Dr. Kaiser's medical review, and Dr. Guo's statistical review. The clinical and statistical teams have concluded that the submitted data support efficacy and safety of Perforomist in COPD patients. I concur with that recommendation.

The pivotal clinical studies mentioned above are briefly reviewed in the following sections. The design and conduct of these studies are briefly described, followed by efficacy and safety findings and conclusions.

Design and conduct of the studies:

Dose ranging studies (studies DL-052 and DL-057):

Study DL-052 was double-blind, placebo- and active-controlled, single-dose, five-way crossover in design, conducted in 7 centers in the United States, in 39 patients with COPD. Enrolled patients received five individual double-blind single day treatments in five periods with 2-7 day washouts between treatment days. The double-blind treatments were Perforomist 40 mcg and 80 mcg administered with a Pari LC Plus nebulizer, Foradil Aerolizer 12 mcg and 24 mcg, and placebo. Serial spirometry was done after treatments for assessment of efficacy. The primary efficacy endpoint was mean percent change in FEV1 over 12 hours. Safety assessments included recording of adverse events, ECGs, and clinical laboratory measures.

Study DL-057 was double-blind, placebo- and active-controlled, single-dose, seven-way crossover in design, conducted in 7 centers in the United States, in 47 patients with COPD. Enrolled patients received seven individual double-blind single day treatments in five periods with 3-8 day washouts between treatment days. The double-blind treatments were Perforomist 2.5, 5, 10, 20, and 40 mcg administered with a Pari LC Plus nebulizer, Foradil Aerolizer 12 mcg and 24 mcg, and placebo. Serial spirometry was done after treatments for assessment of efficacy. The primary efficacy endpoint was mean percent change in FEV1 over 12 hours. The analytical plan called for a step down approach to establish equipotent doses of Foradil Aerolizer 12 mcg and Perforomist. Safety assessments included recording of adverse events, ECGs, and clinical laboratory measures.

12-week efficacy and safety study (study 201-065):

Study 201-065 was double-blind, double-dummy, multiple-dose, placebo- and active-controlled, parallel group in design conducted in 38 centers in the United States. Study subjects were 40 years of age and older, with a clinical diagnosis of COPD, 10 pack-year cigarette smoking history, baseline FEV1 of 70% or lower, and FEV1/FVC of 70% or less. The treatment arms were Perforomist 20 mcg administered by Pari LC Plus jet nebulizer and Pari ProNeb compressor, Foradil Aerolizer 12 mcg, and placebo, each administered twice daily. Primary efficacy variable was FEV1. Serial spirometry was done at baseline, and at weeks 4, 8, and 12. Primary efficacy endpoint was standardized area-under-the curve FEV1 over 12 hours following morning dose of study medication at week 12. Other notable efficacy variables included rescue albuterol use, and St. George's Respiratory Questionnaire (SGRQ). The study was designed to have 115 patients per treatment arms to give 90% power to detect a difference of 0.172 liters difference in standardized AUC 0-12 hours between Perforomist and placebo at a two-sided alpha-level of 0.05. Safety assessment included recording of adverse events, vital signs, physical examination, clinical laboratory measures, ECG, and Holter monitoring. A total of 351 patients were randomized approximately equally to the three treatment arms and 73.7-86.2% patients completed the study, with more discontinuations in the placebo arm.

One-year safety study (study DL-059):

Study DL-059 was originally intended as the efficacy and safety study. It had two periods, a 12-weeks double-blind period, followed by a 40-week open-label safety period. The double-blind period was similar in design to study 201-065 described above, except that the study proposed to enroll 690 COPD patients randomized 2:2:1 to Perforomist 20 mcg, Foradil Aerolizer 12, mcg, and placebo. Unfortunately a major randomization error occurred during the double-blind period of the study making any efficacy determination impossible make. Upon realization of the randomization error, Dey terminated the double-blind phase of the study and re-randomized patients to 52-week open-label treatment with Perforomist 20 mcg, and Foradil Aerolizer 12 mcg, both doses twice daily. The modified intent of the study was to primarily provide long-terms safety data. Safety assessment included recording of adverse events, vital signs, physical examination, clinical laboratory measures, and ECG. The open-label period included 463 patients treated with Perforomist 20 mcg and 106 patients treated with Foradil Aerolizer.

Efficacy findings and conclusion:

The submitted studies support efficacy of Perforomist at a dose of 20 mcg twice-daily in patients with COPD.

In the dose-ranging study DL-052 both the doses of Perforomist tended to show greater efficacy response compared to the Foradil Aerolizer 12 mg dose (data not shown). Dey subsequently conducted the second dose-ranging study DL-057 exploring lower doses of Perforomist. As shown in Table 1, in this study all active treatment arms were superior to

placebo for the primary efficacy endpoint, and the Perforomist 20 mcg dose was numerically comparable to Foradil Aerolizer 12 mcg dose in a pre-specified analysis plan. Dey selected the Perforomist 20 mcg dose to carry forward to confirmatory efficacy and safety studies. Dey's selection of a dose from the dose-ranging study was reasonable. The clinical pharmacology study DL-056 also is supportive of the 20 mcg dose.

In the 12-week study Perforomist 20 mcg was statistically superior to placebo and had comparable numerical response to Foradil Aerolizer 12 mcg dose for the primary endpoint (Table 2) and some secondary endpoints (data not shown). Timed serial FEV1 curve at the first day of dosing and at week 12 showed convincing efficacy of the 20 mcg twice-daily dose. The timed FEV1 curve showed a comparable onset, extend, and duration of bronchodilation with Foradil Aerolizer. On analysis of the FEV1 time response curve following the first dose the median time to onset of bronchodilation as defined by FEV1 increase of 15% was 11.7 minutes, and as defined by FEV1 increase of 12% and 200 ml was 13.1 minutes. The time to onset analyses was based on 78% of patients who responded with a 15% or more increase in FEV1 from baseline. Rescue albuterol use was consistently less in the formoterol treatment arms, as would be expected in such a study. SGRQ data also showed favorable response. The LS mean (95% CI) difference from placebo in the change from baseline to week 12 in SGRQ was -4.9 (—) for Perforomist and -3.5 (—) for Foradil Aerolizer. Although the SGRQ result reached the MID and was statistically significant, this specific data will not be described in the label. Inclusion of results of this important parameter would require replication in another well conducted study.

b(4)

Throughout the clinical program Perforomist was delivered via a Pari LC Plus nebulizer and a PARI ProNeb compressor. The product label will state that Perforomist must be used with a standard jet nebulizer and air compressor and not with nebulizers that can substantially change the delivery characteristics and the ultimate delivered dose.

Table 1. Study DL-057, AUC 0-12 hr (L) results from the dose-ranging studies

Treatment arms	n	Mean	Min, Max
Placebo	47	0.1	
Foradil Aerolizer 12 mcg	47	2.3	
Perforomist 2.5 mcg	47	1.4	
Perforomist 5 mcg	47	1.3	
Perforomist 10 mcg	47	1.9	
Perforomist 20 mcg	47	2.3	
Perforomist 40 mcg	47	3.0	

b(4)

Table 2. Study 201-065, Standardized mean FEV1 AUC 0-12 hrs (L), ITT population

Treatment	n	Baseline	Week 12		Difference from placebo	
			Mean	LS Mean	LS mean	95% CI
Perforomist 20 mcg	123	1.32	1.51	1.49	0.19	0.12, 0.25
Foradil 12 mcg	114	1.28	1.49	1.51	0.21	0.14, 0.27
Placebo	114	1.32	1.33	1.31		

Dey chose not to _____ From a regulatory standpoint such a choice is acceptable. Availability of formoterol inhalation solution with the established efficacy of formoterol in asthma raises the possibility that this product will likely be used in patients with asthma, particularly in pediatric patients with asthma in emergency and urgent care settings. This issue was discussed at a CDER regulatory briefing for a related application (Sepracor's NDA 21-912, arformoterol inhalation solution for COPD) and by unanimous consensus it was agreed that Sepracor should conduct such a program. This issue was discussed with Dey during the review of the NDA and Dey acknowledges this potential use. On the Division's recommendation, Dey has agreed to initially study the safety of arformoterol inhalation solution in pediatric patients 12 years of age and younger with asthma, and study efficacy in the setting of acute use. Both pediatric asthma studies will be phase 4 commitment studies. Until successful completion of an asthma indication, use in patients with asthma will be a limitation for use under the dosage and administration section of the label.

b(4)

Safety findings and conclusion:

The submitted studies support safety of Perforomist at a dose of 20 mcg BID in patients with COPD.

The overall safety database for Perforomist is relatively small. Safety information primary comes from the 12-week efficacy and safety study 21-065 and the 52-week open-label safety study DL-057. In study 21-065 a total of 123 patients were exposed to Perforomist 20 mcg, and in study DL-057 a total of 463 patients were exposed to Perforomist 20 mcg. The relatively small safety database is acceptable because Dey has reasonably linked the Perforomist 20 mcg to Foradil Aerolizer 12 mcg.

In the clinical program there were a total of 8 deaths. Review of the deaths did not raise any specific concerns for Perforomist. Serious adverse events were not common and not of types that raise specific concerns for Perforomist. Cardiac safety assessment did not raise any specific concerns. ECGs and 24-hour Holter monitoring were done in the pivotal efficacy study and ECGs were done in the safety study. Cardiac safety database was adequate. Comparative systemic exposure between Perforomist and Foradil Aerolizer at the recommended doses also two lends further assurance from a systemic safety perspective.

One of the known safety concerns with LABA is asthma related deaths. For this specific serious safety concern, labeling changes were recently made for salmeterol and formoterol, two other members of this class. Labeling changes included addition of boxed warning and medication guide for products containing these drugs. It is unknown whether increased death risk with LABA applies to COPD patients because no large safety studies have been done with LABA in COPD patients. This was discussed at a CDER regulatory briefing for a related application (Sepracor's NDA 21-912, arformoterol inhalation solution for COPD) and there was a unanimous consensus that the arformoterol product label should have a boxed warning and medication guide relating asthma related death. Arformoterol was recently approved with boxed warning

and medication guide. Perforomist will also have similar boxed warning and medication guide.

The question on whether a Company developing a LABA specifically for COPD should be asked to do a large simple COPD safety study post-approval was also discussed at a CDER regulatory briefing for a related application (Sepracor's NDA 21-912, arformoterol inhalation solution for COPD). There was a unanimous consensus that such a study should be conducted, and Sepracor has committed to do such a study with arformoterol. A large simple COPD safety study will be a phase 4 commitment study for Perforomist as well.

Data Quality, Integrity, and Financial Disclosure

DSI audited three sites during review of the application. These were routine inspections and the sites were recommended by the clinical review team based on the importance of the studies and large numbers of subjects enrolled at these sites. All sites were from the critical efficacy study 201-065. The results of the DSI audit showed that in general the sites adhered to the applicable regulations and good clinical practices governing conduct of clinical investigations. During review of the submission no irregularities were found that would raise concerns regarding data integrity. No ethical issues were present. All studies were performed in accordance with accepted clinical standards. The applicant submitted acceptable financial disclosure statements.

Pediatric Considerations

COPD is an adult disease, therefore, specific pediatric studies would not be required that relate to this action specific to COPD. Dey will conduct studies in pediatric asthma patients as phase 4 commitments as mentioned above.

Labeling

Dey submitted a label in the Physician Labeling Rule format and with language that generally conforms with labeling of other products of this class, specifically with the labeling of Foradil Aerolizer and Brovana Inhalation Solution. Review of the label was done by various disciplines of the Division, and on consult by OSE, DDMAC, and PLR group. Various changes to different sections of the label were done to better reflect the data and better communicate the finding to health care providers. Warning statements, including boxed warning and medication guide were added with language consistent with other drugs of this class with some changes reflective of the fact that the indication is specific to COPD. The Division and Dey have agreed to the final version of the label.

Product Name

Dey submitted the three tradenames for this product. These were Perforomist, _____, and _____ in order of preference. DDMAC and DMETS objected to the tradename _____ because of its promotional nature in Spanish translation, but found Perforomist acceptable. This Division also finds the tradename Perforomist acceptable.

b(4)

Action

Dey has submitted adequate data to support approval of Perforomist for maintenance treatment of bronchoconstriction in patients with COPD, including chronic bronchitis and emphysema. The action on this application will be TENTATIVE APPROVAL because of outstanding legal issues as discussed in the Administrative and Introduction section of this memorandum.

As discussed above Dey has agreed to conduct phase 4 studies to evaluate the safety and efficacy of arformoterol inhalation solution in pediatric patients with asthma, and a large simple safety study in patients with COPD.

**APPEARS THIS WAY
ON ORIGINAL**

.....
Uj jt ljt !blsf qsf t f oubypo!pqbolf rfduspojdl!sf dpse!u bux bt !t jhof e!f rfduspojdbm!boe
u jt !qbhf ljt lu f !n bojg t ubypo!pqu f !f rfduspojdl!t jhobw!sf /
.....

! 0t 0

.....
Cbesvm Di pxei vsz
503803118! 14; 26; 18! QN
NFEJDBM PGGJDFS
Ej w! Ej s! t vnnbsz! sf wj f x

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT

Dey, L.P.

DATE OF SUBMISSION

28 June 2006

TELEPHONE NO. (Include Area Code)

707-224-3200

FACSIMILE (FAX) Number (Include Area Code)

707-224-1364

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):

2751 Napa Valley Corporate Drive
Napa, CA 94558

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

NA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) **NDA 22-007**

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)

Formoterol Fumarate

PROPRIETARY NAME (trade name) IF ANY

NA

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any)

Formoterol Fumarate dihydrate

CODE NAME (if any)

NA

DOSAGE FORM:

Solution

STRENGTHS:

20 mcg/2 mL

ROUTE OF ADMINISTRATION:

Inhalation

(PROPOSED) INDICATION(S) FOR USE:

Long-term, twice daily (morning and evening) administration in the maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema.

APPLICATION INFORMATION

APPLICATION TYPE

(check one)

NEW DRUG APPLICATION (21 CFR 314.50)

ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)

BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE

505 (b)(1)

505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Foradil® Aerolizer®

Holder of Approved Application Novartis

TYPE OF SUBMISSION (check one)

ORIGINAL APPLICATION

AMENDMENT TO PENDING APPLICATION

RESUBMISSION

PRESUBMISSION

ANNUAL REPORT

ESTABLISHMENT DESCRIPTION SUPPLEMENT

EFFICACY SUPPLEMENT

LABELING SUPPLEMENT

CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT

OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: NA

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY

CBE

CBE-30

Prior Approval (PA)

REASON FOR SUBMISSION

Initial NDA

PROPOSED MARKETING STATUS (check one)

PRESCRIPTION PRODUCT (Rx)

OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 DVD

THIS APPLICATION IS

PAPER

PAPER AND ELECTRONIC

ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Refer to attached Establishment Information sheet

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND Formoterol Fumarate Inhalation Solution

DMF

IND 68,782 Formoterol Fumarate Inhalation Solution (COPD)

DMF

NDA 20-831 and 21-279 Foradil®

DMF

DMF 19202 Formoterol Fumarate Dihydrate (MDC)

b(4)

This application contains the following items: (Check all that apply)

<input type="checkbox"/>	1. Index
<input checked="" type="checkbox"/>	2. Labeling (check one) <input checked="" type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input checked="" type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input checked="" type="checkbox"/>	4. Chemistry section
<input checked="" type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input checked="" type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input checked="" type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input checked="" type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input checked="" type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input checked="" type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input checked="" type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input checked="" type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input checked="" type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input checked="" type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input checked="" type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input checked="" type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input checked="" type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input checked="" type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input checked="" type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input type="checkbox"/>	20. OTHER (Specify)

CERTIFICATION

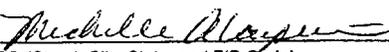
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Michelle A. Carpenter, JD Vice President, Regulatory & Clinical Affairs	DATE: 28 June 2006
ADDRESS (Street, City, State, and ZIP Code) 2751 Napa Valley Corporate Drive, Napa, CA 94558		Telephone Number (707) 224-3200 x4750

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions; searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Date: August 17, 2006

From: Jeanne M. Delasko, RN, MS
Label Initiatives Specialist
Study Endpoint and Label Development (SEALD)
Office of New Drugs, CDER

Through: Laurie B. Burke, RPh, MPH
Director, SEALD

To: Akilah Green, MS, BSN, RN
Senior Regulatory Management Officer, DPAP

Subject: Proposed Labeling Format Review
NDA 22-007 (formoterol fumerate)

This memo provides a list of revisions for the proposed labeling that should be conveyed to the applicant in the 74-day letter. Please contact me at 796-0146 with questions or concerns.

Highlights:

- The verbatim highlights limitation statement that must appear at the beginning of Highlights is the following: **These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).** Insert the name of the drug product and not the entire phrase "TRADE NAME (formoterol fumarate) 20 mcg/2 mL". In addition, delete the word "of" in your highlights limitation statement. [See 21 CFR 201.57(a)(1)]
- The drug names must be followed by the drug's dosage form and route of administration. Do not include the dose (i.e., 20 mcg/ 2mL). [See 21 CFR 201.57(a)(2)]
- Under Dosage and Administration, change " _____," to "_____". [See 21 CFR 201.57(a)(7)]
- In the beginning of the labeling after the drug names, you indicate the dosage form as a "solution." However, under Dosage Forms and Strengths, the dosage form is omitted. Indicate the correct dosage form. [See 21 CFR 201.57(a)(8)]
- For adverse reactions reporting, leave out the parentheses [i.e., use 1-800-429-7751 not (1-800-429-7751)]. [See 21 CFR 201.57(a)(11)]
- You have submitted a Patient Package Insert with your application. Therefore, the patient counseling information statement must state: **See 17 for PATIENT**

COUNSELING INFORMATION – and FDA approved patient labeling.
[See 21 CFR 201.57(a)(14)]

- A revision date must be placed at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, the date will be determined by the month/year of approval.
- When the labeling is in final draft, the Highlights must be limited in length to one-half page, in 8 point type. [See 21 CFR 201.57(d)(8)]
- A horizontal line must separate the Highlights, Contents, and Full Prescribing Information. [See 21 CFR 201.57(d)(2)]
- Please submit the completed Structured Product Labeling (SPL) Highlights Data Elements Table. To complete the Highlights Data Elements Table, please refer to the following two documents at the FDA Data Standards Council website (<http://www.fda.gov/oc/datacouncil>) under SPL: “Companion Document for SPL Release 2 Implementation Guide for Highlights DRAFT” and “SPL Highlights Data Element Table.” This table must be filled out with the terms that have been proposed for the Highlights data elements. The companion document provides information on the terminology to be used. If you need assistance completing the Highlights data elements portion of your application, please contact spl@fda.hhs.gov.

Full Prescribing Information: Contents:

- The Agency recommends the use of a two-column format for the Full Prescribing Information: Contents. [Implementation Guidance]

Full Prescribing Information (FPI):

- Regarding Drug Abuse and Dependence, is this information necessary? If clearly inapplicable, you can omit. [See 21 CFR 201.56(d)(4)]
- The manufacturer information should be located after Patient Counseling Information section, at the end of labeling. [Best Practices]

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

/s/

Jeanne Delasko
8/23/2006 10:32:29 AM
CSO

Lilliam Rosario
8/23/2006 12:55:31 PM
PHARMACOLOGIST

Laurie Burke
8/23/2006 06:51:42 PM
INTERDISCIPLINARY



NDA 22-007

NDA ACKNOWLEDGMENT

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

Attention: Michelle A. Carpenter, JD
Vice President, Regulatory and Clinical Affairs

Dear Ms. Carpenter:

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

Name of Drug Product: Formoterol Fumarate Inhalation Solution, 20 mcg/2 mL
Review Priority Classification: Standard (S)
Date of Application: June 28, 2006
Date of Receipt: June 29, 2006
Our Reference Number: NDA 22-007

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 28, 2006 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be April 29, 2007.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application. Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call Ms. Akilah, Senior Regulatory Management Officer, at (301) 796-1219.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Chief Regulatory Project Manager
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Akilah Green
8/18/2006 02:59:19 PM
Signed for Sandy Barnes

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
 FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE
 COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS DEY LP Michelle Carpenter 2751 Napa Valley Corporate Drive Napa CA 94558 US	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 22-007
--	--

2. TELEPHONE NUMBER 707-224-3200-4750	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:
--	--

3. PRODUCT NAME Formoterol Fumarate Inhalation Solution, 20 mcg/2 mL	6. USER FEE I.D. NUMBER PD3006513
---	--------------------------------------

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

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act	<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
--	--	--

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE <i>Michelle A. Carpenter</i>	TITLE VP, Regulatory & Clinical Affairs	DATE 5/26/06
--	--	-----------------

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
 \$767,400.00

Form FDA 3397 (12/03)

CONFIDENTIAL



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

Date: October 20, 2005

To: Michelle A. Carpenter V.P., Regulatory Affairs and Clinical Development	From: Akilah Green, RN, MS Regulatory Management Officer
Company: Dey, L.P.	Division of Pulmonary and Allergy Drug Products
Fax number: 707-224-1364	Fax number: 301-796-9718
Phone number: 707-224-3200 X4750	Phone number: 301-796-1219

Subject: IND 68,782 September 20, 2005, PreNDA meeting minutes

Total no. of pages including cover: 12

Comments:

Document to be mailed: YES NO

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, or a person authorized to deliver this
 document to 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 have received this document
 in error, please notify us immediately by telephone at
 (301) 827-1050. Thank you.

MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 20, 2005
TIME: 3:00 – 4:30 PM
LOCATION: Food and Drug Administration
APPLICATION: IND 68,782/ Formoterol Fumarate Inhalation Solution /Dey
Type B/PreNDA Meeting

DEY L.P. REPRESENTATIVES:

Muhammad Asif, Ph.D., Director, Analytical Development
Gina Capiaux, Ph.D., Manager, Clinical and Publishing
Michelle Carpenter, J.D., Vice President, Clinical and Regulatory Affairs
Imtiaz Chaudry, Ph.D., Senior Vice President, Scientific Affairs
Antoinette Douglas, Manager, Regulatory CMC and Toxicology

DIVISION OF PULMONARY AND ALLERGY PRODUCTS (DPAP) REPRESENTATIVES:

Badrul A. Chowdhury, M.D., Ph.D., Division Director
Peter Starke, M.D., Clinical Team Leader
John H. Gunkel, M.D., Clinical Reviewer
Anthony Durmowicz, M.D., Clinical Reviewer
Timothy Robison, Ph.D., Pharmacology/Toxicology Reviewer
Chong Ho Kim, Ph.D., Chemistry, Manufacturing, and Controls Reviewer
Prasad Peri, Ph.D., Chemistry, Manufacturing, and Controls Reviewer
Ted Guo, Ph.D., Biostatistics Reviewer
Ruthanna Davi, M.S., Biostatistics Team Leader
Emmanuel Fadiran, Ph.D., Clinical Pharmacology and Biopharmaceutics Team Leader
Shinja Kim, Ph.D., Clinical Pharmacology and Biopharmaceutics Reviewer
Akilah Green, Regulatory Project Manager

BACKGROUND: Dey submitted a Type B meeting request dated July 27, 2005, to discuss issues related to the submission of an NDA in electronic common technical document (eCTD) format. Dey also submitted a briefing package dated August 9, 2005, which contained a list of questions to be discussed at this meeting. Upon review of the briefing package, the Division responded to Dey's questions via facsimile correspondence on September 14, 2005. The content of that fax is printed below. Any discussion that took place at the meeting is captured directly under the relevant original response including any changes in our original position. Dey's questions are in *bold italics*; FDA's response is in *italics*; discussion is in normal font.

1.1 Administrative

1.1.1 *As agreed upon in prior meetings with the Agency, a 505(b)(2) NDA cross-referencing the Foradil NDAs will be submitted for Formoterol Fumarate Inhalation Solution 20 mcg/2 mL. The anticipated NDA filing date is June of 2006. Does the Agency anticipate any legal changes to the status of 505(b)(2) NDAs that would affect this strategy?*

FDA Response:

505(b)(2) applications have come under legal challenge, but more specific information about the status is unavailable at this time.

1.1.2 *For the purpose of this briefing package, a detailed outline of the proposed NDA (eCTD format) is provided. Does the Agency have any comment on the proposed content or organization of the NDA?*

FDA Response:

- *Modules 2-5 need an n.1 pdf Table of Contents(ToC). Each Module (with the exception of Module 1) needs to be able to be referenced with a hyperlinked comprehensive module specific ToC.*
- *It appears that you are going to populate section "1.6 Meetings" with "historical" data. This section, for the initial submission, should remain empty. It is used to request a meeting and provide subsequent material to the requested meeting. Historical meeting data, if necessary, should be worked into Module 2 Summaries.*
- *Module 2 appears "heavy". Module 2 is intended to house "summaries" – rationale, reasoning, arguments and conclusions to support the application, not as a data analysis podium. Think of it as an "executive summary" of the data and analyses contained in Modules 3-5.*

Based on Dey's understanding of the eCTD requirements and as indicated in the ICH Harmonized Tripartite Guideline, M4 - Organization of the Common Technical Documents for the Registration of Pharmaceuticals for Human Use, the module specific (n.1) Table of Contents (TOCs) "are only called for in the paper version of the CTD; there is no entry needed for the eCTD". Additionally, inclusion of .pdf versions of the module specific (n.1) TOCs in the eCTD would require the use node extensions which are "discouraged and should be done when there is no other feasible means to submit information" per the ICH M2 EWG Electronic Common Technical Document Specification document (V 3.2 February 02, 2004). Dey requested that the Agency confirm this request and if needed provide technical guidance as to where this information should be provided within the xml backbone? The Division responded that while there is no "requirement" for the pdf TOC, some reviewers find it advantageous. Dey correctly noted that we misstated the location for the PDF TOC. If Dey decides to provide a pdf TOC (not required) it would be worked into the first document of each Module, *not n.1*, as remarked earlier.

Again, the pdf TOC is *not* required, but, desired by some. If you choose not to include

one because of complexity or cost, it will not affect reviewability of your submission. The comments were observations on certain aspects of Dey's submission. As put forth in the meeting package, the submission is acceptable (with the exception of "history" that Dey indicated they would include in Module 1).

1.2 Clinical

1.2.1 As per discussions and agreement with the Agency, the following Chronic Obstructive Pulmonary Disease (COPD) clinical studies will be submitted in the NDA to support approval of 20 mcg/2 mL and 20 mcg/0.5 mL FFIS. Please confirm successful completion of the pivotal safety and efficacy studies and pharmacokinetic study will support NDA approval.

FDA Response:

The studies appear to be satisfactory from a clinical perspective to permit filing of the application. Approvability will be determined by review of the application.

1.2.2 Because of the randomization error that occurred in the double-blind portion of Clinical Study DL-059 which resulted in patients receiving inconsistent medications throughout the 12-week period and based on the 13 April 2005 correspondence from the Agency, no efficacy data will be presented for this study. Please confirm the Agency agrees.

FDA Response:

The Division concurs that efficacy data from study DL-059 will not be presented.

1.2.3 As agreed with the Agency, due to the randomization error that occurred in the initial double-blind portion of Clinical Study DL-059, the study was amended to primarily provide long-term safety data and the 12-week efficacy study was repeated. Does the Agency agree with the appropriateness of providing separate clinical study reports for the double-blind and open-label safety data for Clinical Study DL-059.

FDA Response:

Providing separate study reports is acceptable, although not necessary; however, we expect the two portions of the study to be integrated in the Summary of Clinical Safety.

The Division acknowledged the difficulty in integrating the safety data from the two studies because of the errors in dispensing the study medications, but encourages Dey to make an attempt to integrate the safety data. One possible method is to integrate according to the medication actually received, i.e., by the intervals of treatment and duration of exposure. Dey noted that they will list the adverse events separately and then integrate all Phase III studies (the two 12 week studies and the open label study). The Division recommended that adverse event data from the double-blind portion of DL-059 not be included in the table of adverse events in the labeling; however, the long-term

safety data from that study will have to be referenced because it is the only long-term data available.

1.2.4 *Due to the randomization error that occurred in the double-blind portion of Clinical Study DL-059, Dey is proposing to analyze the data for safety based on four-week treatment intervals to address the majority of patients switching treatments at re-supply. It is anticipated this data will be integrated with the safety data for all COPD studies if the data is consistent with other studies. However, in the event there are inconsistencies likely to be related to lack of a wash-out period between groups, the data will not be integrated and will be presented separately. Does the Agency agree?*

FDA Response:

Present the data both separately and integrated. The Division will determine whether there is "consistency" or not, and the possible reasons if there is inconsistency. In any case, data from DL-059 should not be integrated with the other COPD studies in the adverse event table(s) presented in the package insert.

1.2.5 *Dey is proposing to analyze data from the pivotal efficacy study, Clinical Study 201-065, according to the Statistical Analysis Plan provided in Section 7. Does the Agency agree that the resulting analyses will support NDA approval?*

FDA Response:

The Division agrees with the methods prescribed in the statistical analysis plan for Study 201-065. Regarding approvability, the results of this statistical analysis, along with the other information submitted in the NDA, will be carefully evaluated by the Division as part of the NDA review process.

1.26 *Dey is proposing to analyze data from the one-year open-label portion of Clinical Study DL-059 according to the Statistical Analysis Plan provided in Section 7. Does the Agency agree that the resulting analyses will support NDA approval?*

FDA Response:

The Division acknowledges the revision of the study objectives from demonstrating the efficacy and safety of FFIS to only obtaining safety data. The safety report based on the open-label data may be useful as part of the overall safety evaluation. Regarding approvability, these results, along with the other information submitted in the NDA, will be carefully evaluated by the Division as part of the NDA review process.

1.27 *Dey is proposing to analyze data from the double-blind portion of Clinical Study DL-059 according to the Statistical Analysis Plan provided in Section 7. Does the Agency agree that the resulting analyses will support NDA approval?*

FDA Response:

The Division agrees that the methods prescribed in the statistical analysis plan for the double blind portion of Study DL-059 seem reasonable. However, the usefulness of this safety data is in question and will be addressed as part of the NDA review since delineation of the actual treatment effect will not be straightforward in this setting.

- 1.28** *As written in the protocol and SAP for the pivotal efficacy study, 201-065, the last non-missing post-baseline measurement prior to Week 12 will be used for the primary efficacy endpoint, standardized absolute AUC_(0-12h) (L) for FEV₁, when the Week of 12 measurement is missing. Does the agency agree?*

FDA Response:

The Division, in principle, agrees with the LOCF approach for calculating FEV₁. Sensitivity analyses will be used to assess the impact of the imputation for the missing observations.

- 1.2.9** *Dey proposes to cross-reference the Foradil NDAs for the formoterol fumarate clinical data in Module 2.5 Clinical Overview and where appropriate in Module 2.7 Clinical Summary. Dey further proposes to only summarize key relevant formoterol fumarate literature in these sections and to provide copies of these references in Module 5.4. Dey proposes to provide a complete bibliography in Module 2.5.7 and commit to provide the Agency with any requested literature within 72 hours of request. Does the Agency agree with this proposal?*

FDA Response:

The proposal is acceptable.

With regard to the summary of the literature, the Division commented that Dey's major reference should be to the Foradil NDA, not to literature. If Dey wishes to do so, citing additional articles is also acceptable. The Pharmacology/Toxicology review team is in agreement with this.

The Division advised Dey to be sure to address the issue of the safety of the long-acting beta-agonists, which was recently considered at the Pulmonary and Allergy Products Advisory Committee meeting. The consideration of this issue by the Agency will be ongoing. In the NDA, Dey should discuss the advisory committee meeting and the relevant discussions that took place regarding safety and whether or not it applies to formoterol fumarate. Dey would also be well advised to consider a benefit/risk analysis and/or a risk management plan on this issue.

- 1.2.10** *Dey proposes to submit the clinical data to the Agency for the NDA in SAS transport files that are version 5 compliant. Does the Agency have any comment on this proposal?*

FDA Response:

The proposal is acceptable.

1.2.11 *It is our understanding that if SAS datasets are provided for clinical studies, the individual patient data listings in Section 16.4 of the Clinical Study Reports are not needed. Dey is planning on submitting SAS datasets for all CSRs included in the NDA in lieu of sending the individual patient data listings in Section 16.4. Does the Agency agree?*

FDA Response:

The Division agrees; however, we request that you submit patient profiles for patients who died, discontinued due to adverse events, or experienced serious adverse events.

1.2.12 *Pursuant to 21 CFR 314.50(f)(2), Dey plans to submit the Case Report Forms for patients who died, discontinued from the study due to an adverse event or experienced a serious adverse event. Does the Agency agree?*

FDA Response:

The Division agrees.

1.2.13 *Dey will be conducting several Phase IIIb and line extension studies with formoterol fumarate while the NDA is under review. Dey proposes to submit available serious adverse events reported in these studies in the 120-day NDA safety report, in addition to the IND. Does the Agency agree?*

FDA Response:

The Division agrees.

1.3 Nonclinical

1.3.1 *As agreed upon with the Agency, data from the following toxicology studies will be submitted in the NDA to support NDA approval and the qualification of the formoterol fumarate desformyl analog impurity/degradant. Based on published literature, formoterol fumarate desformyl analog is also believed to be a metabolite.*

- *Maximum tolerate dose study in rats*
- *14-Day inhalation study in rats*
- *90-Day inhalation toxicity study in rats to quantify formoterol fumarate desformyl analog at a minimum of a 10X multiple of the clinical dose*
- *Ames test of formoterol fumarate desformyl analog*

Please confirm successful completion of these studies will support NDA approval and qualification of the formoterol fumarate desformyl analog related compound.

FDA Response:

Pending review, successful completion of these studies will support NDA approval and qualification of the formoterol fumarate desformyl analog.

As a general note, genotoxicity studies should be conducted with the isolated impurity/degradant rather than the spiked impurity/degradant; however, this is not an issue for the proposed NDA. Formoterol and desformoterol contain the same basic structural alert (i.e., aromatic amine). Formoterol was negative in the standard battery of genotoxicity tests.

- 1.3.2** *The 90-day inhalation study in rats to qualify formoterol fumarate desformyl analog was designed in collaboration with the Agency to qualify this impurity at a level of at least — in the drug product. Please confirm successful completion of the study will support qualification at a level of at least —*

b(4)

FDA Response:

From a nonclinical perspective, successful completion of the study will support qualification at a level of at least — However, it should be noted from a CMC perspective, this could be considered inappropriate based upon manufacturing capability.

b(4)

- 1.3.3** *Dey proposes to cross-reference the Foradil® NDAs (21-279 and 20-831) for formoterol fumarate nonclinical data in Module 2.4 Nonclinical Overview and where appropriate in Module 2.6 Nonclinical Written and Tabulated Summaries. Dey further proposes only to summarize key relevant formoterol fumarate literature in these sections and to provide copies of these references in Module 4.3. Dey proposes to provide a complete bibliography of all references in the public domain in Module 2.6 and commit to provide requested literature within 72 hours of request. Does the Agency agree with this proposal?*

FDA Response:

Refer to the response to Question 1.2.9.

1.4 Chemistry, Manufacturing, and Controls

- 1.4.1** *For the 2 mL drug product, Dey is proposing an expiration dating of 24 months under refrigerated conditions (—). During the 24 months, the product can be held at room temperature conditions for up to 3 months. The proposed expiration date is based on up to 18 months of stability at ICH conditions for refrigerated (5 ± 3 °C) products. To support the in-use period, an additional 3 months of room temperature data (25 ° ± 2 °C/60% ± 5%RH) will be provided. Does the Agency agree with this proposal?*

b(4)

FDA Response:

This is a review issue that can only be determined when the full set of stability data are provided in the NDA submission. You will need to justify with data; your

proposed expiry at the long term refrigerated storage condition, over wrapped at room temperature (dispensed), and at room temperature in-use (unwrapped) using appropriate long term, accelerated, and relevant supportive stability data.

- 1.4.2 The proposed expiration date for the _____ mL FFIS product will be the same as the 2 mL. The NDA will contain up to 9 months of stability data at ICH conditions for refrigerated ($5 \pm 3^\circ\text{C}$) products as well as 6 months of stability data under accelerated ($25^\circ \pm 2^\circ\text{C}/60\% \pm 5\%\text{RH}$) conditions. Dey proposes to amend the NDA during review with up to 18 months of refrigerated data. Does the Agency agree with this proposal? b(4)

FDA Response:

New GRMP guidelines provide for compressed review timelines which rely upon complete initial NDA submission. Any amendment submitted after the initial submission may not be reviewed. Therefore, provide all stability data necessary to support approval, expiry, dispensed, and in-use periods in the original submission.

- 1.4.3 Dey has qualified an alternate active Pharmaceutical ingredient (API) vendor for formoterol fumarate according to FDA Guidance for Industry BACPAC 1: Intermediates in Drug Substance Synthesis Bulk Activities Post Approval Changes: Chemistry, manufacturing and Controls Documentation, February 2001. In the NDA, Dey will submit significantly more drug product stability data than is required under BACPAC 1 for an alternative vendor. Based on this data, Dey proposes an expiration date of 24 months for product manufactured with API from the alternate vendor. Does the agency agree?

FDA Response:

The acceptability of a 24 months expiry will depend on the extent and quality of the stability data submitted.

For new vendors we typically see multiple batches of data for drug substance. It is to Dey's advantage to have more data. The Division questioned, if one of the batches is off, how will Dey justify the difference. The Division commented that it appears that Dey is doing a 6-month study for drug substance. The all data necessary for review must be provided at the time of NDA submission. We do not accept comparability protocols prior to NDA approval. Dey should pursue the NDA then upon approval submit a supplemental NDA. This is a review issue. 12-months of stability data is the minimum requirement for an 18-month expiry.

1.5 Proposed Package Inserts

- 1.5.1 Does the Agency have any comment on the proposed strategy for development of the package insert for 20 mcg/2 mL FFIS and _____? b(4)

FDA Response:

See the response to question 1.5.2.

1.5.2 The proposed package insert for _____ 1L FFIS, which contains

b(4)

FDA Response:

The Division discourages marketing different concentrations of products which deliver the same dose because there is the potential to confuse users of the products and cause dosing errors. For example, patients might erroneously fill the nebulizer with multiple vials of FFIS _____, rather than dilute one vial, resulting in an overdose with possibly catastrophic consequences.

If you wish to pursue this approach, include within the Risk Management Plan your proposals for assuring that the different dosage forms will be correctly used.

The Division questioned Dey's reasoning for selecting two different concentrations for formoterol fumarate and their plans for ensuring patient safety. Dey stated that the different concentrations would be preferred by physicians and consumers, according to their market research. They went on to specify that the _____ would be most used by hospital pharmacies. Dey further stated that they had not considered special plans for ensuring patient safety.

b(4)

The Division reiterated its concerns about the possibility for catastrophic errors if two concentrations were to be marketed. The Division encouraged Dey to reconsider this issue. If Dey wants to pursue different concentrations, the Division's recommendation would be to do it by filing a supplemental NDA for the second concentration. If Dey chooses to pursue two concentrations in one application, however, the Division stated that the NDA should address the potential safety issues.

Additional CMC Comments:

b(4)

b(4)

A single response is provided for the next three questions.

- 1.5.3 In the 13 April 2005 letter from FDA to Dey regarding the proposed package insert/analysis of safety data the Agency indicated that the adverse events from the asthma studies with 20 mcg/2 mL FFIS should not be included in the package insert unless "a safety finding could cut across indications. This issue should be revisited at the time of the pre-NDA meeting." In the dose-ranging asthma studies adverse events reported were largely unremarkable and most not considered related to study medications. In all but one study (DL-055) the doses evaluated in these trials were 2 to 10 times (40-244 mcg/2 mL) the dose proposed for marketing (20 mcg/2 mL). It is the opinion of Dey that asthma adverse events are not appropriate for inclusion in the labeling for a COPD indication. Does the Agency agree?*
- 1.5.4 The proposed package inserts will include adverse events observed in Dey's clinical studies and not adverse event information from the Foradil package insert. Does the Agency agree?*
- 1.5.5 Given Dey's product will not be indicated for asthma, Dey believes the inclusion of a black box warning for FFIS, similar to that which was proposed in the July 2005 Advisory Committee meeting is not appropriate. Does the Agency agree?*

FDA Response:

Specific answers to your questions cannot be given at this time. The safety of long-acting beta-agonists will be a subject of intense scientific and regulatory scrutiny over the coming months and years, and it is possible that concern about their use will extend to COPD patients, in addition to asthma patients. The Division will keep Dey informed about any developments that might affect its product. Include in the NDA a Risk Management Plan, which describes your plans to assure that FFIS use will be limited to COPD patients and how you plan to prevent its use by asthma patients.

Dey indicated that they are not planning to have a risk management plan; rather they plan to address this issue in the risk/benefit section of the NDA. The Division left that decision up to Dey.

The Division questioned whether Dey could safely market their product to COPD patients, while assuring that the product was not used by asthma patients in whom the LABA safety signals have been seen. History does not support the use of the label as a sufficient way to target the use of a drug for one population and exclude another. Dey noted that they initially began developing the use of formoterol fumarate in asthma patients, however, based on available resources they decided to pursue the COPD indication because more COPD patients prefer nebulizers than asthma patients. Marketing the product to asthma patients would be difficult because patients would need to be convinced to switch to a nebulizer. The Division recommended that Dey make this argument in their NDA. However, Dey cannot ignore the possibility of asthma patients using their drug. Unintended use of the product in pediatric patients is of particular concern because they are at a greater risk for serious exacerbations. These are serious issues to consider with regard to whether or not the drug can be safely marketed.

Akilah Green,
Regulatory Management Officer

Drafted by: Green/October 18, 2005
Initialed: Kim, C.H./October 18, 2005
Lostritto/October 19, 2005
Robison/October 18, 2005
Sun/October 18, 2005
Kim, S./October 19, 2005
Gunkel/October 19, 2005
Starke/October 19, 2005
Chowdhury/October 20, 2005
Finalized: Green/October 20, 2005

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

/s/

Akilah Green

10/20/2005 02:42:26 PM



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

Date: January 11, 2005

To: Mike Rinehart Director, Regulatory and Clinical Affairs	From: Akilah Green Regulatory Project Manager
Company: Dey, L.P.	Division of Pulmonary and Allergy Drug Products
Fax number: 707-224-1364	Fax number: 301-827-1271
Phone number: 707-224-3200 X3483	Phone number: 301-827-5585

Subject: IND 68,782 December 15, 2004, minutes of teleconference

Total no. of pages including cover: 5

Comments:

Document to be mailed: YES XNO

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, or a person authorized to deliver this document to 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 have received this document in error, please notify us immediately by telephone at (301) 827-1050. Thank you.

Memorandum of Telephone Facsimile Correspondence

Date: January 11, 2005

To: Mike Rinehart
Director, Regulatory and Clinical Affairs

Fax: 707-224-1364

From: Akilah Green
Regulatory Project Manager

Subject: IND 68,782 Formoterol Fumarate Inhalation Solution, 20 mcg
December 15, 2004, meeting minutes

Reference is made to the meeting held between representatives of your company and this Division on December 15, 2004. Attached is a copy of our final minutes for that meeting. These minutes will serve as the official record of the meeting. If you have any questions or comments regarding the minutes, please call me at (301) 827-5585.

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 FDA, 5600 Fishers Lane, HFD-570, DPADP, Rockville, MD 20857.

Thank you.

MEMORANDUM OF TELECONFERENCE

Meeting Date: December 15, 2004
Time: 12:30-12:45 pm
Application: IND 68,782 Formoterol Fumarate Inhalation Solution, 20 mcg

BETWEEN:

Name: Imtiaz Chaudry, Ph.D., Senior Vice President, Scientific Affairs
Gerald Klein, M.D., VP, Medical Affairs and Clinical Research
Michelle Carpenter, J.D., VP, Regulatory and Clinical Affairs
Mike Rinehart, Director, Regulatory and Clinical Affairs
Meg O'Brien, Manager, Regulatory and Clinical Affairs
Nicholas J. Gross, M.D., Section Chief, Pulmonary Section Hines VA **b(4)**

Phone: 1-866-448-6758
Representing: Dey, L.P.

AND

Name: Badrul A. Chowdhury, M.D., Ph.D., Division Director
Eugene Sullivan, M.D., Deputy Division Director
Peter Starke, M.D., Clinical Team Leader
John Gunkel, M.D., Clinical Reviewer
Sue Jane Wang, Ph.D., Acting Statistics Team Leader
Ted Guo, Ph.D., Statistics Reviewer
Akilah Green, Regulatory Project Manager
Representing: Division of Pulmonary and Allergy Drug Products, HFD-570

SUBJECT: To discuss Dey's discontinuation of the Phase III clinical trial due to the inadvertent use of two different randomization codes.

BACKGROUND:

This teleconference was held to follow up a submission from Dey reporting an error in the randomization system in their Phase III study of Formoterol Fumarate Inhalation Solution for COPD. The study was planned for a 12-week randomized phase with a 9-month safety extension. A change in the randomization code had been made in the course of planning the study, but Dey discovered well into the study that both the original and revised codes were erroneously being implemented. As a result, the patients who had been enrolled in the study thus far represented a mixture of two different randomization schemes. This would invalidate efficacy results, but the safety assessments could still be used. Dey's proposal was to discontinue the randomized phase of the study and begin again in a new 12-week randomized

efficacy study of the same design and objectives. Meanwhile, the patients enrolled to date would continue on in an open-label phase for a total of 12 months to provide the necessary exposure to assess safety. Patients continuing on would not be re-randomized.

DISCUSSION:

Dey reported that they have randomized 695 patients to date and of the 695, only 25 received medication according to the intended randomization code. So few patients randomized correctly, precluded the possibility of obtaining any meaningful efficacy data from the study.

The Division stated that we have reviewed Dey's submission and understand Dey's plan in principal. We cannot comment on the specifics of the plan, but we have no objections to the general approach described above. Dey stated that they intend for the new 12-week efficacy study to mirror the previous protocol and questioned whether the Division would be willing to review the study design prior to beginning the study. The Division responded that Dey should submit the protocol to the IND. However, it is not necessary to request a review prior to implementation if it is substantively the same as the protocol previously reviewed by the Division.

Dey questioned whether they could alter the sample size slightly to be consistent with the altered approach to the safety evaluations described above. Dey also indicated that they still plan to have an active comparator arm in the safety study. The Division stated again that Dey's plans are reasonable. The Division pointed out that Dey is the most knowledgeable about its overall program and the general approach they have proposed is acceptable to the Division.

Akilah Green
Regulatory Project Manager

cc:

HFD-570/Division Files
HFD-570/Starke
HFD-570/Gunkel
HFD-570/Gou
HFD-570/Wang
HFD-570/Chowdhury
HFD-570/Green

Drafted by: Green/December 23, 2004
Initialed: Gunkel/January 7, 2005
Starke/January 7, 2005
Guo/January 6, 2005
Wang/January 6, 2005
Chowdhury/January 11, 2005
Finalized: Green/January 11, 2005

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

/s/

Akilah Green

1/11/05 02:19:59 PM



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

Date: April 20, 2004

To: Mike Rinehart Director, Regulatory and Clinical Affairs	From: Akilah Green, RN Regulatory Project Manager
Company: Dey, L.P.	Division of Pulmonary and Allergy Drug Products
Fax number: 707-224-1364	Fax number: 301-827-1271
Phone number: 707-224-3200 X3483	Phone number: 301-827-5585

Subject: IND 68,782 April 2, 2004, EOP2 Meeting Minutes

Total no. of pages including cover: 24

Comments:

Document to be mailed: YES XNO

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, or a person authorized to deliver this document to 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 have received this document in error, please notify us immediately by telephone at (301) 827-1050. Thank you.

Memorandum of Telephone Facsimile Correspondence

Date: April 20, 2004

To: Mike Rinehart
Director, Regulatory and Clinical Affairs

Fax: 707-224-1364

From: Akilah Green, RN
Regulatory Project Manager

Subject: IND 68,782/Formoterol Fumarate Inhalation Solution/Dey
April 2, 2004, meeting minutes

Reference is made to the meeting held between representatives of your company and this Division on April 2, 2004. Attached is a copy of our final minutes for that meeting. These minutes will serve as the official record of the meeting. If you have any questions or comments regarding the minutes, please call me at (301) 827-5585.

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 FDA, 5600 Fishers Lane, HFD-570, DPADP, Rockville, MD 20857.

Thank you.

MEMORANDUM OF MEETING MINUTES

DATE: April 2, 2004
TIME: 8:00-9:30AM
LOCATION: Food and Drug Administration, Parklawn Building,
5600 Fishers Lane, Rockville, MD 20857,
Twinbrook Conference Room
APPLICATION NUMBER: IND 68,782/Formoterol Fumarate Inhalation
Solution/Dey L.P.

DEY, L.P. REPRESENTATIVES:

Imtiaz Chaudry, Ph.D., Senior Vice President, Scientific Affairs
Gerald Klein, M.D., Vice President, Medical Affairs and Clinical Research
Paul Laskar, Ph.D., Senior Director, Pharmaceutical Development
Gabriel Lebovic, Ph.D., Director, Regulatory CMC and Toxicology
Mike Rinehart, Director, Regulatory and Clinical Affairs
Meg O'Brien, Manager, Regulatory and Clinical Affairs

CONSULTANTS TO DEY, L. P.

DIVISION OF PULMONARY AND DRUG PRODUCTS (DPAP) REPRESENTATIVES:

Badrul A. Chowdhury, M.D., Ph.D., Division Director
Eugene Sullivan, M.D., Deputy Director
J.Harry Gunkel, M.D., Clinical Reviewer
Richard Lostritto, Ph.D., Chemistry Team Leader
Chong Ho Kim, Ph.D., Chemistry Reviewer
C. Joe Sun, Ph.D., Pharmacology/Toxicology Team Leader
Timothy Robison, Ph.D., Pharmacology/Toxicology Reviewer
Emmanuel Fadiran, Ph.D., Clinical Pharmacology and Biopharmaceutics Team Leader
Shinja Kim, Ph.D., Clinical Pharmacology and Biopharmaceutics Reviewer

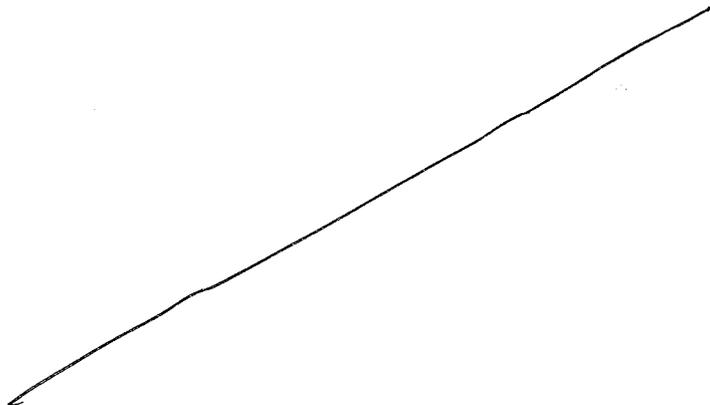
b(4)

Mahboob Sobhan, Ph.D., Acting Biostatistics Team Leader
Ted Guo, Ph.D., Biostatistics Reviewer
Akilah Green, Regulatory Project Manager

BACKGROUND: Dey submitted a meeting request for a Type B End of Phase II meeting dated January 7, 2004, to discuss their Phase III clinical study and clinical development plan in support of a 505(b)(2) New Drug Application for formoterol fumarate Inhalation Solution. The meeting package was dated February 27, 2004.

DISCUSSION:

Slide 1



b(4)

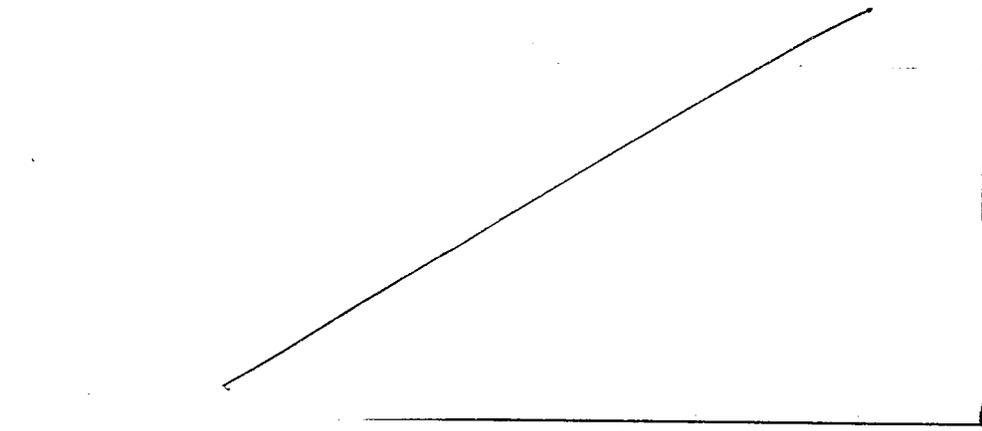
1 Page(s) Withheld

 Trade Secret / Confidential (b4)

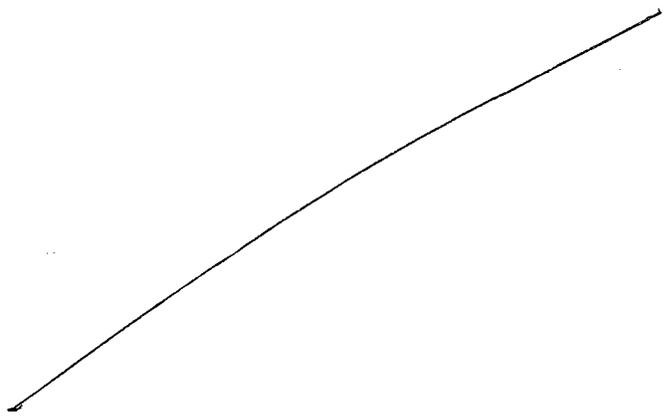
 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

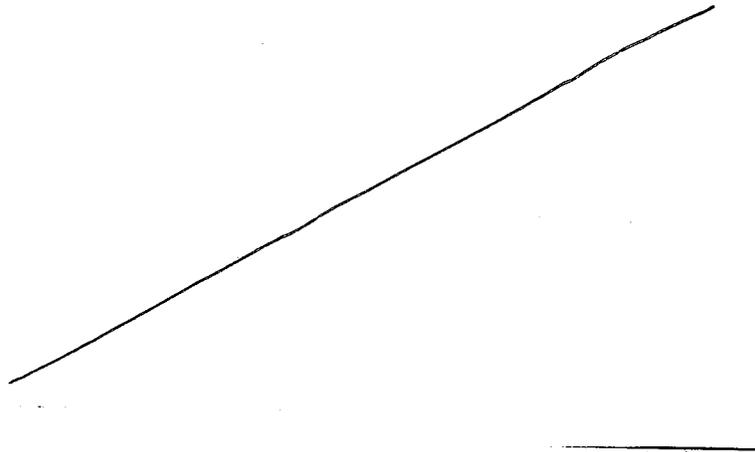


b(4)

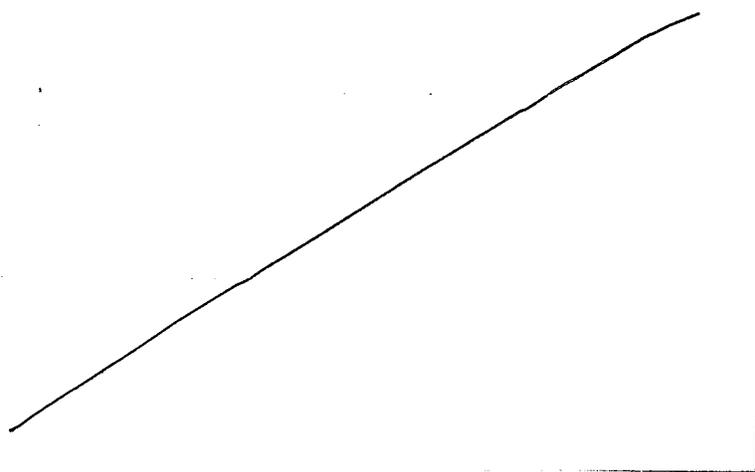


b(4)

The Division emphasized the limitations that will be imposed on label claims by performing only a single study, and asked Dey to consider this in their final planning. The absence of independent substantiation of various aspects of the drug's performance will hamper the ability to provide as much information as possible to the prescriber and patient in the product label.



b(4)



b(4)

Dey asked if the Division's recommendation represents a new general requirement for controlled long-term safety data. The Division noted that this is a strong recommendation, not an absolute requirement. While there is no precedent for an absolute requirement, the Division feels that it would be in Dey's best interest to include a control group in the long term study. The Division pointed out that it is quite likely that

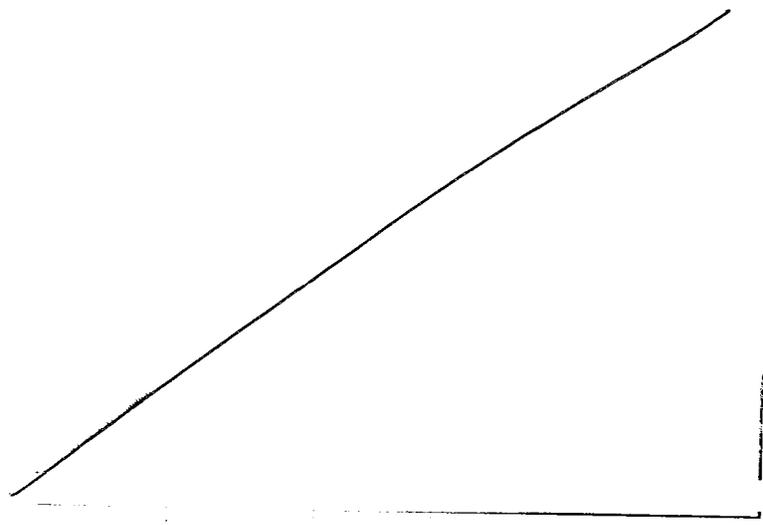
serious and non-serious adverse events will occur in this patient population during the course of the long-term study. In the absence of a control group, it would be very difficult to be sure that observed events were not related to the investigational drug. The Division also stated that our request is consistent with requests made of other sponsors in the past.

Dey asked what minimum number of patients would be required in the comparator arm. The Division indicated that there is no specific number; it is Dey's decision to determine how many patients are needed, keeping in mind the role that the control arm will serve. Dey asked if the patients in the placebo group could be treated with Foradil during the long-term extension. The Division restated its recommendation that there be an active comparator arm, but indicated that there could be several possible approaches to achieving this. The Division stated that Dey should develop a reasonable approach, and that the Division will be happy to review it and respond to any questions.

b(4)

The Division stated that reference to the use of multiple nebulizers in the product label would require adequate supportive data. Use of different nebulizers may be associated with potentially clinically significant differences in drug performance. A small study

would probably be insufficient; pharmacokinetic as well as efficacy and safety data would be needed. Dey noted that its question is concerned with low volume nebulizers like those named in the question. For use in those devices, Dey is considering developing a drug product that would contain the same quantity of drug substance, but would be more concentrated in a smaller volume. The Division indicated that this would represent a distinct drug product, which would require its own development program.



The Division recommended that Dey describe clinical criteria for COPD, rather than use the ATS definition.

The Division noted that Dey should generate sufficient data to allow accurate description of the 12-hour FEV₁ curve for the product. That task is made more difficult because of the different modes of delivery and the resulting need for a double-dummy design. Post-dose serial FEV₁ will presumably be timed from the completion of both treatments. Therefore, the timing of the post-dose spirometry will not accurately reflect the time since completion of treatment with the first of the two treatments. This is particularly relevant with formoterol, because of its relatively rapid onset of action. Dey should consider how they wish to describe their product's effect and plan the sequence of the

two drugs accordingly, noting that a description of the performance of the investigational drug is most important for the product label. This issue could limit comparability to Foradil.

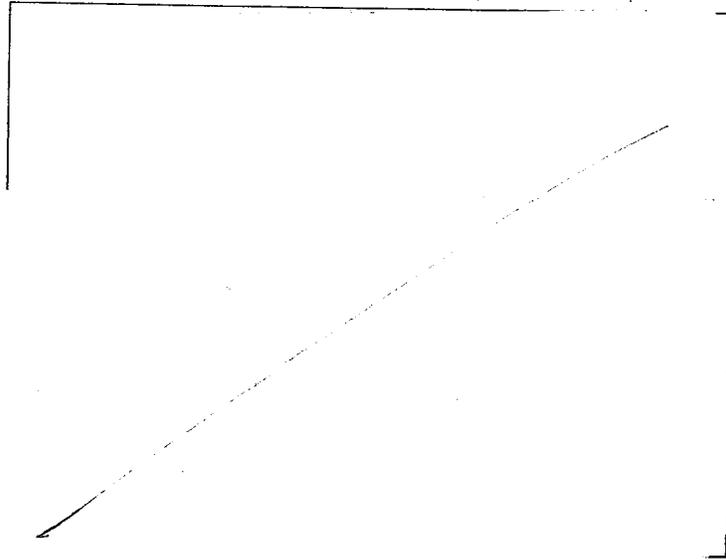
b(4)

b(4)

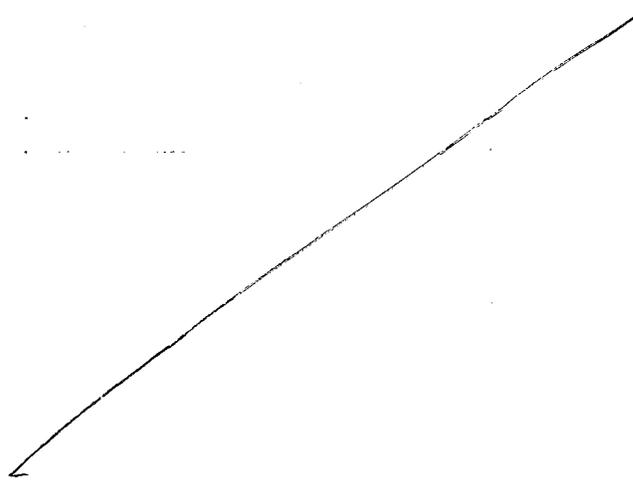
Dey noted that there is no way to take the "CG" marking off of the Foradil capsules, therefore Dey wanted to place a similar marking on the placebo capsule so that both

capsules appear similar to assist with the blinding. However, if they place "CG" on the placebo capsule, the capsule would be misbranded, so the vendor is reluctant to place the "CG" on the placebo capsule. The Division stated that Dey is correct with regard to their statement about misbranding. Dey indicated that the "G" on the Foradil capsule is subtle so they hope that the "CC" marking will not be noticeably different. The Division stated that placing a different marking on the placebo can potentially cause problems with the blind. Dey should therefore query some of the study subjects and ask them which medication they think they received to provide some assurance that the study blind was maintained.

The Division clarified that our recommendation is that Holter monitoring should be performed in 100-200 patients on the investigational drug. Dey should determine the number of patients needed to randomize in order to achieve that number on study drug, in addition patients in control groups. Both short-term and long term (12-week) Holter data are requested.



b(4)



b(4)

The Division added that it is up to Dey to select the covariates to include in the statistical model but too many factors may be costly.

The Division further suggested that Dey may wish to consider exploring more than one dose in the Phase III trial. If the PK study (DL-056) suggests that systemic exposure is greater with FFIS 20mcg than with Foradil 12mcg, it may prove helpful to have controlled clinical safety data with a higher dose.

3 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

The Division noted that we received Draft Final Reports for the 4-Day Range Finding Inhalation Study with Rats and 14-Day Inhalation Toxicology Study with Rats as well as Toxicokinetic data for formoterol and desformoterol from the 14-Day study by e-mail. We have made a preliminary examination of these materials.

1 Page(s) Withheld

 Trade Secret / Confidential (b4)

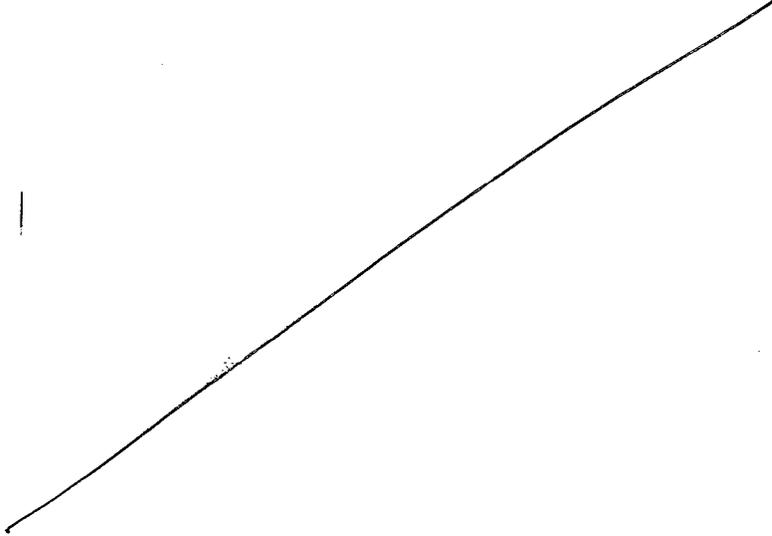
 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

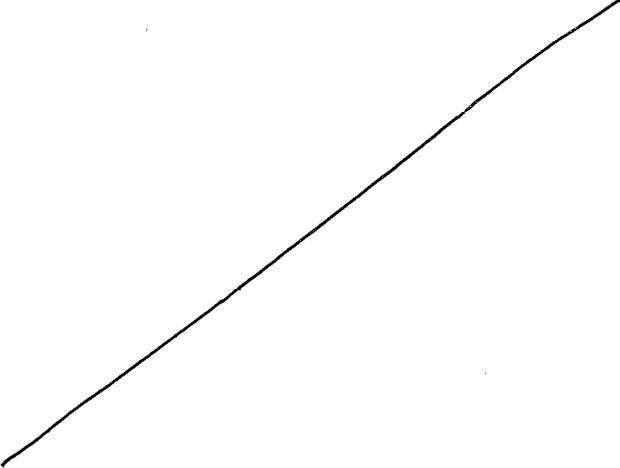
Dey noted that they envision having a unit dose vial. The Division noted that this is a poorly defined point and Dey should specify, with data, any room temperature "dispensed" period (overwrapped) as well as any unoverwrapped (i.e., removed) "in-use" period. Dey indicated that they plan on studying the room temperature "dispensed" and "in-use"

periods starting with overwrapped drug product aged to various fractions of expiry storage.

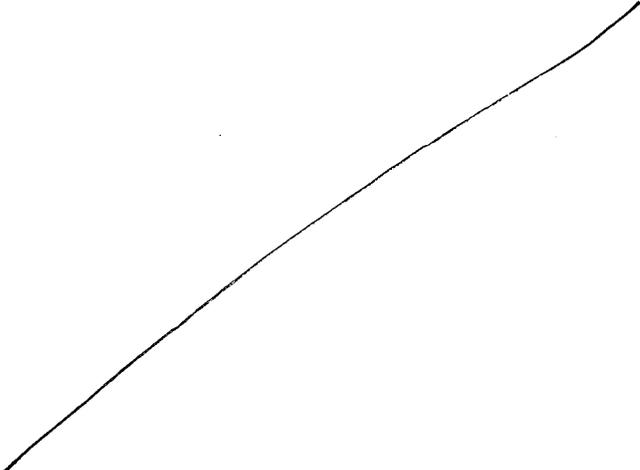


b(4)

Dey indicated that they have no plans for performing long-term stability for the unoverwrapped (i.e., overwrap removed) container. The Division noted that the label should specify the duration of time the medication is useable once the overwrap is removed. There is an issue of loss of formulation, as well as exposure to the environment (e.g., oxygen and other ingress), because of the permeable nature of the LDPE container. Any proposed interval should be supported by data.



The Division further noted that the three sigma approach is not automatic and may not be the best depending on many factors. Dey and the Agency have to look at the totality of data. The more data Dey provides the better; lesser use of extrapolations is preferred.



The Division informed Dey that it is their decision whether or not they want to perform 24 hour room temperature stability unoverwrapped (i.e., overwrap removed) studies compared to overwrapped. If Dey desires a —-hour unopened indication, this will need to be supported with appropriate data.

b(4)

Dey noted that they plan to submit up to 18-months of data and extrapolate. The Division stated that going beyond 18-months will be difficult to justify on a scientific basis. Dey indicated that they plan to conduct these studies starting with fresh and aged drug product near expiry.

The Division further noted that Dey should ensure that they are specific about what the DMF holders are doing for them and that there is no disconnect in what Dey wants the DMF holders to do and what the DMF holders are actually doing on Dey's behalf. As Dey finalizes their data, they should inform the Division if they would like to have a follow-up CMC meeting.

The Division questioned whether Dey planned to use a different nebulizer for clinical use. If so, the package will change. Dey stated that the vial will contain less than 0.5ml

of a more concentrated solution and will remain a single unit dose. Dey indicated that they plan to provide stability data and all of the required CMC data to support it. The Division noted that Dey's concentrated formulation drug product will be considered as a new drug product.

POST MEETING DISCUSSION:

The Division originally communicated that desformoterol might be qualified by demonstrating that it is a major systemic metabolite from the 14-Day inhalation toxicity study with rats. From the preliminary toxicokinetic data, it appears that desformoterol constituted approximately 20-25% of the total exposure. In a reconsideration of this issue, the Division has concerns that demonstrating desformoterol as a major systemic metabolite does not address issues regarding its potential local toxicity in the lung given concerns for the intended treatment population and the susceptibility of the respiratory airways to injury. Desformoterol can be formed by nonenzymatic metabolism. It is suggested that in vitro metabolism of formoterol in rat bronchoalveolar lavage fluid at 37°C be assessed over a 1-hr period. A range of formoterol concentrations should be examined (e.g., at least 3 concentrations of formoterol). Human bronchoalveolar lavage fluid would also be acceptable. If substantial in vitro generation of desformoterol can be demonstrated, further study would not appear to be needed. However, if there is only minor or negligible in vitro generation of desformoterol, the Dey will need to conduct a 90-day inhalation toxicology study with desformoterol in the rat since the drug product will be administered on a chronic basis.

Akilah Green
Regulatory Project Manager

cc:

HFD-570/Division Files
HFD-570/Gunkel
HFD-570/Sullivan
HDD-570/Fadiran
HFD-570/Kim
HFD-570/Robison
HFD-570/Sun
HFD-570/Kim
HFD-570/Lostritto
HFD-570/Sobhan
HFD-570/Guo
HFD-570/Chowdhury

Drafted by: Green/April 9, 2004
Initialed: Lostritto/April 12, 2004
Kim, C./April 12, 2004
Kim, S./April 14, 2004
Fadiran/April 14, 2004
Sullivan/April 15, 2004
Gunkel/April 15, 2004
Robison/April 19, 2004
Sun/April 19, 2004
Chowdhury/April 19, 2004
Finalized: Green/April 20, 2004

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

/s/

Akilah Green

4/20/04 09:09:28 AM

ACTION PACKAGE CHECKLIST

Application Information		
BLA # NDA # 22-007	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type
Proprietary Name: Established Name: Formoterol Fumarate Dosage Form: Inhalation Solution 20 mcg/2 mL		Applicant: Dey, L.P.
RPM: Akilah Green		Division: Pulmonary and Allergy Products Phone # 301-796-1219
NDAs: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)		505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): NDA 20-831 Foradil Aerolizer Inhalation Powder and NDA 21-279 Foradil Aerolizer Inhalation Powder Provide a brief explanation of how this product is different from the listed drug. This application provides for a change in dosage form, from inhalation powder to inhalation solution. <input type="checkbox"/> If no listed drug, check here and explain: Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct. <input type="checkbox"/> Confirmed <input checked="" type="checkbox"/> Corrected Date: October 30, 2006
❖ User Fee Goal Date ❖ Action Goal Date (if different)		April 29, 2007
❖ Actions		
• Proposed action		<input type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (<i>specify type and date for each action taken</i>)		<input checked="" type="checkbox"/> None
❖ Advertising (<i>approvals only</i>) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (<i>indicate dates of reviews</i>)		<input type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

❖ Application Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 5	
NDAs, BLAs and Supplements: <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2 <input type="checkbox"/> Orphan drug designation	
NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies	BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies
NDAs and NDA Supplements: <input type="checkbox"/> OTC drug	
Other: Other comments:	
❖ Application Integrity Policy (AIP)	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> Exception for review (<i>file Center Director's memo in Administrative Documents section</i>) OC clearance for approval (<i>file communication in Administrative Documents section</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action 	<input type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

<p>within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</i></p>	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) (indicate date for each review)	
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (indicate date)	
Labeling	
❖ Package Insert	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	April
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	March 28, 2007
<ul style="list-style-type: none"> • Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	June 28, 2006
❖ Patient Package Insert	
<ul style="list-style-type: none"> • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	March 23, 2007
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	January 25, 2007
<ul style="list-style-type: none"> • Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	June 28, 2006
❖ Medication Guide	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	March 23, 2007
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	March 28, 2007
<ul style="list-style-type: none"> • Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling) 	January 25, 2007
❖ Labels (full color carton and immediate-container labels)	
<ul style="list-style-type: none"> • Most-recent division-proposed labels (only if generated after latest applicant submission) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling 	March 28, 2006

❖ Labeling reviews and minutes of any labeling meetings (<i>indicate dates of reviews and meetings</i>)	<input checked="" type="checkbox"/> DMETS May 15, December 12, and 21, 2006, and February 7, 2007 <input checked="" type="checkbox"/> DSRCS February 28, 2007 <input checked="" type="checkbox"/> DDMAC February 6, and March 9, and 202007, <input checked="" type="checkbox"/> SEALD August 23, 2006 <input type="checkbox"/> Other reviews <input type="checkbox"/> Memos of Mtgs
---	---

Administrative Documents

❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) (<i>indicate date of each review</i>)	September 14, 2006, March 22, 2007
❖ NDA and NDA supplement approvals only: Exclusivity Summary (<i>signed by Division Director</i>)	<input type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> • Center Director's Exception for Review memo • If AP: OC clearance for approval 	
❖ Pediatric Page (all actions)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. (<i>Include certification.</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Commitment Studies	<input type="checkbox"/> None
<ul style="list-style-type: none"> • Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>) 	March 29, 2007
<ul style="list-style-type: none"> • Incoming submission documenting commitment 	March 30, 2007
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	August 18, September 11, 21, November 3, 2006, January 29, February 2, 16, March 1, 23, and 29, 2007
❖ Internal memoranda, telecons, email, etc.	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) 	
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date</i>) 	<input type="checkbox"/> No mtg September 20, 2005
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date</i>) 	<input type="checkbox"/> No mtg April 2, 2004
<ul style="list-style-type: none"> • Other (e.g., EOP2a, CMC pilot programs) 	December 15, 2005
❖ Advisory Committee Meeting	<input type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> • Date of Meeting 	
<ul style="list-style-type: none"> • 48-hour alert or minutes, if available 	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	

CMC/Product Quality Information

❖ CMC/Product review(s) (<i>indicate date for each review</i>)	August 1 and 10, 2006, January 12, March 22, 2007
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer (<i>indicate date for each review</i>)	<input type="checkbox"/> None February 6, 2007
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications)	

<ul style="list-style-type: none"> <input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(all original applications and all efficacy supplements that could increase the patient population) <input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>) 	January 12, 2007
<ul style="list-style-type: none"> <input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>) 	
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) (<i>indicate date of each review</i>)	December 4, 2007 <input type="checkbox"/> Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: March 21, 2007 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

<ul style="list-style-type: none"> ❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> Facility review (<i>indicate date(s)</i>) Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>) 	<input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input checked="" type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed

Nonclinical Information

❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	August 24, 2006, February 20, 2007
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	
❖ Nonclinical inspection review Summary (DSI)	<input type="checkbox"/> None requested

Clinical Information

❖ Clinical review(s) (<i>indicate date for each review</i>)	August 31, and September 6, 2006
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	
❖ Clinical consult reviews from other review disciplines/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None
❖ Microbiology (efficacy) reviews(s) (<i>indicate date of each review</i>)	<input type="checkbox"/> Not needed December 14, 2006
❖ Safety Update review(s) (<i>indicate location/date if incorporated into another review</i>)	
❖ Risk Management Plan review(s) (including those by OSE) (<i>indicate location/date if incorporated into another review</i>)	
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date of each review</i>)	<input type="checkbox"/> Not needed
❖ DSI Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested
<ul style="list-style-type: none"> Clinical Studies Bioequivalence Studies Clin Pharm Studies 	February 13, 2007
❖ Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None August 24, 2006
❖ Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None February 21, 2007

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- VERDICT** (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication **AND** a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.