

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-007

CHEMISTRY REVIEW(S)

Perforomist
(formoterol fumarate dihydrate)
NDA 22-007

Summary Basis for Recommended Action
From Chemistry, Manufacturing, and Controls

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

Indication: Formoterol fumarate dihydrate is indicated for the treatment of COPD.

Presentation: Perforomist™ Inhalation Solution is supplied in unit dose, low density polyethylene (LDPE) vials as a clear, colorless, sterile, aqueous solution, and is a single strength of formoterol fumarate (20 mcg in 2mL). The single strength is available in a shelf carton, containing overwrapped, single-use, 2.5 mL vials, each containing either 2.5 or 60 unit dose LDPE vials. **b(4)**

EER Status: Acceptable 21-MAR-2007

Consults:

Biometrics –	Approved 01-FEB-2007
Microbiology –	Approved 04-DEC-2006
Pharm/Tox –	Approved 21-FEB-2007
Methods Validation –	Revalidation by Agency was not requested
EA –	Categorical exclusion granted under 21 CFR §25.31(c)
DDMAC –	No Comments 06-FEB-2007
Trade Name –	Approved 07-FEB-2007

Original Submission: 28-JUN-2006

Post-Approval Agreements: None

Drug Substance

Formoterol fumarate dihydrate is purchased from either ~~_____~~, DMF ~~_____~~ or Merck Development Centre Private Limited, India (DMF 19202). **b(4)**

Formoterol fumarate dihydrate has the chemical name (±)-2-hydroxy-5-[(*IRS*)-1-hydroxy-2-[[(*IRS*)-2-(4-methoxyphenyl)-1-methylethyl]-amino]ethyl]formanilide fumarate dihydrate and a chemical formula of $(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot 2H_2O$.

Formoterol has ~~_____~~ chiral centers and can exist in ~~_____~~ stereoisomeric forms: ~~_____~~ **b(4)**
~~_____~~ The drug substance used in Formoterol Fumarate Inhalation Solution 20 mcg/2 mL is a racemic mixture (R,R and S,S). Formoterol fumarate dihydrate exists as a white to yellowish white solid. It is slightly soluble in water and its aqueous

solubility is pH and temperature dependent. The solubility of Formoterol fumarate dihydrate at room temperature was determined to be _____ mg/mL at pH 3 and _____ ng/mL at pH 5.0 and pH 7.0. The solubility of Formoterol fumarate dihydrate at refrigerated temperature was determined to be _____ mg/mL at pH 5.0.

b(4)

Conclusion: Drug substance is satisfactory

b(4)

Drug product

*Perforomist*TM (formoterol fumarate inhalation solution 20 mcg/2mL) is a sterile, clear isotonic solution for oral inhalation by nebulization. Each 2 mL unit-dose vial contains 20 mcg of formoterol fumarate in _____ USP; _____ / mg of sodium chloride USP to maintain _____ mg of citric acid _____ USP and _____ mg of sodium citrate dehydrate USP to buffer the formulation to pH 5.0. The formulation is packaged in low-density polyethylene (LDPE) unit dose vials by the _____. The sterility assurance of the manufacturing program was evaluated and found acceptable by the microbiology staff. The LDPE vials are individually overwrapped with an _____. The shelf cartons contain either _____ overwrapped vials or 60 overwrapped vials.

b(4)

b(4)

Using a Pari LC PlusTM nebulizer/Proneb® Ultra compressor system, the delivered dose, defined as the amount of formoterol fumarate emitted from the nebulizer was determined to be _____ mcg. The average respirable dose, defined as the amount of Formoterol Fumarate contained in aerosols nebulized from two doses (_____ mL) having aerodynamic diameters in the range of _____ μ m, was _____ mcg. These measured values represent about 37% of label claim. Finally, the volume based median diameter and the span, (D10-D90)/D50, of the Formoterol Fumarate Inhalation Solution 20 mcg/2 mL aerosols determined by _____ were _____ μ m and _____, respectively. The recommended administration route is by inhalation using a nebulizer (with a facemask or a mouthpiece) connected to an air compressor.

b(4)

The applicant has provided appropriate stressed, supporting and real-time stability data to support the proposed expiry period of "24 months under the recommended refrigerated storage condition (_____, including up to 3 months post-dispensing storage at 25°C \pm 2°C/60% RH \pm 3% RH".

b(4)

Conclusion: Drug product is satisfactory.

Additional Items:

All associated Drug Master Files are acceptable or the pertinent information has

been adequately provided in the application.

The analytical methods used in the testing procedures (release, stability and in-process) are well known and widely used by the pharmaceutical industry; revalidation by Agency laboratories will not be requested

Overall Conclusion: From a CMC perspective, the application is recommended for **Approval.**

Blair A. Fraser, Ph.D.
Director, DPA I/ONDQA

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

/s/

Blair Fraser
3/22/2007 05:08:40 AM
CHEMIST



NDA 22-007

**Formoterol Fumarate
(Formoterol Fumarate Dihydrate)**

Dey, L.P.

**John C. Hill, PhD.
ONDQA/DPA-I**



Table of Contents

Table of Contents2

Chemistry Review Data Sheet.....3

The Executive Summary7

I. Recommendations.....7

 A. Recommendation and Conclusion on Approvability7

 B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....7

II. Summary of Chemistry Assessments.....7

 A. Description of the Drug Product(s) and Drug Substance(s)7

 B. Description of How the Drug Product is Intended to be Used.....8

 C. Basis for Approvability or Not-Approval Recommendation.....9

III. Administrative.....9

 A. Reviewer's Signature.....9

 B. Endorsement Block.....9

 C. CC Block9

 Akilah Green, Consumer Safety Officer9

Chemistry Assessment.....10

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....10

 S DRUG SUBSTANCE [Formoterol Fumarate.....10

 Dihydrate, Merck (MDC) and ———]10

 P DRUG PRODUCT [Formoterol Fumarate Inhalation19

 Solution 20 mcg/2 mL].....19

 A APPENDICES66

 R REGIONAL INFORMATION66

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 184

 A. Labeling & Package Insert84

 B. Environmental Assessment Or Claim Of Categorical Exclusion88

b(4)



Chemistry Review Data Sheet

- 1. NDA 22-007
- 2. REVIEW # 1
- 3. REVIEW DATE: 12-JAN-2007
- 4. REVIEWER: John C. Hill, PhD.
- 5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

(N) Original NDA Filing	28-JUN-2006
(BZ) Responses to CMC Filing Comments	28-SEP-2006
(BC) Chemistry Amendment , samples of printed carton	12-OCT-2006
(BL) Labeling Amendment, draft labeling	18-OCT-2006
(BL) Labeling Amendment, draft labeling	19-OCT-2006
(C) Sample drug product final container	27-OCT-2006
(BL) Labeling Amendment, draft labeling	21-NOV-2006

7. NAME & ADDRESS OF APPLICANT:

Name: Dey, L.P.

Address: 2751 Napa Valley Corporate Drive
Napa, CA 94558

Representative: Michelle A Carpeneter, JD
Vice President, Regulatory and Clinical Affairs

Telephone: (707) 224-3200

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None Provided

Chemistry Review Data Sheet

- b) Non-Proprietary Name (USAN): Formoterol fumarate dihydrate
c) Code Name/# (ONDC only): NA
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(2)

Listed Drug: Foradil Aerolizer, Novartis

10. PHARMACOL. CATEGORY: Long-acting selective β 2-adrenergic bronchodilator

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 20 mcg/2ml

13. ROUTE OF ADMINISTRATION: Inhalation

14. Rx/OTC DISPENSED: Rx OTC

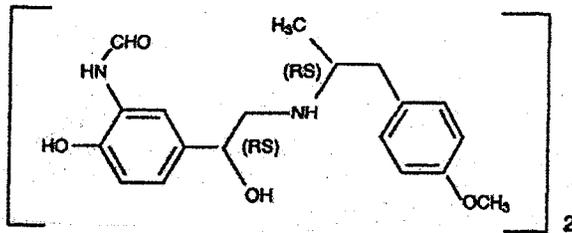
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemistry Review Data Sheet



Molecular Formula: $C_{42}H_{52}N_4O_{12} \cdot 2H_2O$
 $(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot 2H_2O$

Molecular Weight: Formoterol Fumarate Dihydrate = 840.91
 Formoterol base = _____

b(4)

CAS number: CAS-43229-80-7 (Formoterol Fumarate Dihydrate), and
 CAS-73573-87-2 (Formoterol base)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
_____	II	_____	_____	4	Adequate	23-SEP-2005	LOA issued 14-FEB-2006
19202	II	Merck	Formoterol Fumarate Dihydrate	4	Adequate	31-AUG-2006	LOA issued 19-MAR-2006
_____	III	_____	_____	4	Adequate	23-MAR-2001	LOA issued 27-FEB-2006
_____	III	_____	_____	4	Adequate	04-FEB-2000	LOA issued 02-MAR-2006

b(4)

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type I DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")



CHEMISTRY REVIEW



Chemistry Review Data Sheet

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	_____	Formoterol Fumarate Dihydrate Inhalation Solution
IND	68,782	Formoterol Fumarate Dihydrate Inhalation Solution (COPD)
NDA	20-831 (Novartis Pharms)	Foradil Aerolizer
NDA	21-279 (Novartis Pharms)	Foradil Aerolizer

b(4)

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Pending		
Pharm/Tox	Pending		
Biopharm			
LNC			
Methods Validation	Acceptable	20-NOV-2006	John C. Hill, Ph.D.
OPDRA			
EA	Acceptable	20-NOV-2006	John C. Hill, Ph.D.
Microbiology	Approval	01-DEC-2006	Bryan S. Riley, Ph.D.

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. Yes
 No If no, explain reason(s) below:



The Chemistry Review for NDA 22-007

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a CMC viewpoint this application is approvable (AE). The outstanding CMC issues are:

- Acceptable CGMP status for pending pre-approval establishment inspections.
- Acceptable consultative reviews.
- Final labeling review.

The applicant has provided appropriate stressed, supporting and real-time stability data to support the proposed expiry period of:

- 24 months under the recommended refrigerated storage condition (_____).
- Up to 3 months post-dispensing storage at 25°C ± 2°C/60% RH ± 3% RH.

b(4)

Expiration dates may be extended based upon acceptable long-term and post-dispensing data from a minimum of three commercial production batches.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Drug Substance

- None

Drug Product

- None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product

Formoterol Fumarate Inhalation Solution 20 mcg/2mL is a sterile, clear isotonic solution developed for oral inhalation by nebulization. Each 2 mL unit-dose vial contains 20 mcg of formoterol fumarate in _____, _____ mg of sodium chloride to _____ mg of citric acid _____ and _____ mg of sodium citrate dihydrate to buffer the formulation to pH 5.0. The formulation is packaged in low-density polyethylene (LDPE) unit dose vials that are individually overwrapped with an _____. The overwrapped vials are packaged in a shelf carton available in two sizes. One size contains _____ overwrapped vials and the other size contains 60 overwrapped vials.

b(4)

Using a Pari LC Plus™ nebulizer/Proneb® Ultra compressor system, the delivered dose, defined as the amount of formoterol fumarate emitted from the nebulizer was evaluated to be _____

b(4)

Executive Summary Section

mcg. The average respirable dose, defined as the amount of Formoterol Fumarate contained in aerosols nebulized from two doses (2 mL) having aerodynamic diameters in the range of _____ μm, was _____ mcg. These measured values represent about 37% of label claim. Finally, the volume based median diameter and the span, (D10-D90)/D50, of the Formoterol Fumarate Inhalation Solution 20 mcg/2 mL aerosols determined by _____ were _____ μm and _____, respectively. The recommended administration route is via a nebulizer (with a facemask or a mouthpiece) connected to an air compressor.

b(4)

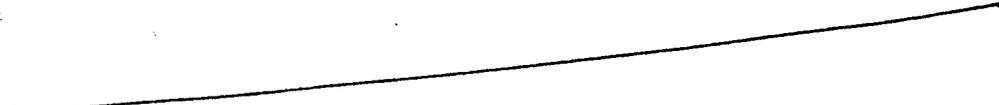
The applicant has provided appropriate stressed, supporting and real-time stability data to support the proposed expiry period of "24 months under the recommended refrigerated storage condition _____ including up to 3 months post-dispensing storage at 25°C ± 2°C/60% RH ± 3% RH". Expiration dates may be extended based upon acceptable long-term and post-dispensing data from a minimum of three commercial production batches.

b(4)

Drug Substance

Formoterol fumarate dihydrate has the chemical name (±)-2-hydroxy-5-[(1*R,S*)-1-hydroxy-2-[[*(1R,S)*-2-(4-methoxyphenyl)-1-methylethyl]-amino]ethyl]formanilide fumarate dihydrate and a chemical formula of (C₁₉H₂₄N₂O₄)₂ · C₄H₄O₄ · 2H₂O. Formoterol has _____ chiral centers and can exist in _____ stereoisomeric forms: _____ The drug substance used in Formoterol Fumarate Inhalation Solution 20 mcg/2 mL is a racemic mixture (R,R and S,S). Formoterol fumarate dihydrate exists as a white to yellowish white solid. It is slightly soluble in water and its aqueous solubility is pH and temperature dependent. The solubility of Formoterol fumarate dihydrate at room temperature was found to be _____ mg/mL at pH 3 and _____ mg/mL at pH 5.0 and pH 7.0. The solubility of Formoterol fumarate dihydrate at refrigerated temperature was found to be _____ mg/mL at pH 5.0. As the therapeutic dose of Formoterol fumarate is in the order of tens of micrograms, Formoterol fumarate dihydrate was demonstrated to have sufficient aqueous solubility in the pH range of 3 - 7 to be developed as an inhalation solution for nebulization.

b(4)



b(4)

The applicant has qualified two commercial vendors as suppliers of formoterol fumarate:

- _____ (DMF _____)
- Merck Development Centre Private Limited, (DMF 19202)

b(4)

These Drug Master Files have been reviewed and are awaiting responses from the DMF holders for final CMC evaluation. Formoterol fumarate from both vendors is compliant with current pharmacopeial specifications for Formoterol fumarate. The applicant has provided adequate chemical and structural data which indicate that formoterol fumarate obtained from either vendor is interchangeable in the final Formoterol Fumarate Inhalation Solution 20 mcg/2 mL drug product.

B. Description of How the Drug Product is Intended to be Used

Formoterol is a potent and long acting selective β₂-adrenoreceptor agonist which has been shown to be effective in the management of asthma and chronic obstructive pulmonary disease (COPD). Formoterol Fumarate Inhalation Solution 20 mcg/2 mL is a unit dose, ready-to-use product intended for the treatment of COPD. Formoterol Fumarate Inhalation Solution is intended for long-term, twice daily (morning and evening) self-administration by nebulization for the



Executive Summary Section

maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema.

The drug product is delivered to the patient using a nebulizer with a facemask or mouthpiece, connected to an air compressor.

C. Basis for Approvability or Not-Approval Recommendation

This application is approvable (AE) from a CMC viewpoint. This recommendation is based upon the evaluation of the drug substance characterization data, the drug product pharmaceutical and manufacturing development data, and the accelerated, stressed and real-time stability data. The applicant has demonstrated lot-to-lot consistency in the manufacture and the quality of the drug product. However, labeling and consultative reviews, and satisfactory CGMP facility inspections are pending.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

John C. Hill, Ph.D., Review Chemist, DPA-I: Same date as electronic review
Blair Fraser, Ph.D., Director, DPA-I: Same date as electronic review

C. CC Block

Akilah Green, Consumer Safety Officer
Scott Goldie, Project Manager for Quality

79 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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

/s/

John C. Hill
1/12/2007 01:51:28 PM
CHEMIST

Blair Fraser
1/12/2007 02:44:50 PM
CHEMIST

OND Division of Pulmonary and Allergy Products

NDA: 22-007

Stamp Date: 29-Jun-2006

Applicant: Dey LP

PDUFA Date: 29-Apr-2007

Proposed Proprietary Name: None provided

Established Name: Formoterol Fumarate

Dosage form and strength: Inhalation Solution (20 mcg/ 2 mL (vial)).

Route of Administration: oral inhalation

Indications: 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.

Pharmacologic Class: Long-acting selective β 2-adrenergic bronchodilator (LABA)

PAL: Prasad Peri, Ph.D. Branch 2/DPA I/ONDQA

Fileability recommendation: Acceptable for filing

Review team recommendation: Single primary reviewer (John Hill, Ph.D)

Time goals:

- **Initial Quality Assessment in DFS:** by 31-Jul-2006 (NDA accessible on 13-July-2006)
- **Chemistry filing memo in DFS:** by 31-Jul-2006
- Filing decision "Day 45": 13-Aug-2006 (tentative; to be set by Clinical Division)
- Filing review issues "Day 74": 11-Sept-2006 (tentative; to be set by Clinical Division)
- **Chemistry Review (DR/IR) letter:** by 29-Nov-2006
- Mid-cycle meeting "Month 5": 28-Nov-2006 (tentative; to be set by Clinical Division)
- **Final Chemistry Review "Month 8" in DFS:** by 28-Feb-2007
- PDUFA: 29-Apr-2007

Related Documents

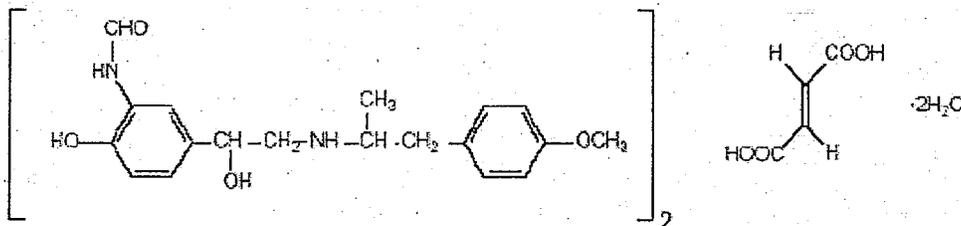
Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND: _____
IND 68,782 Formoterol Fumarate Inhalation Solution (COPD)
NDA 20-831 and 21-279 Foradil[®]
DMF 1: _____
DMF 19202 Formoterol Fumarate Dihydrate (MDC)

DMF
DMF

b(4)

Structural Formula



CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharm/ClinPharm	To be determined by Primary Reviewer
CDRH	<i>Not Applicable</i>
EA	To be assessed by Primary Reviewer
EES	EER sent to Office of Compliance on 17/18-JUL-2006
DMETS	<i>Labeling consult request will be sent as part of DPAP's request.</i>
Methods Validation	<i>Validation may be requested of FDA labs after test methods are finalized.</i>
Microbiology	<i>A consult will be sent to evaluate the sterility assurance program</i>
Pharm/Tox	<i>To be sent immediately to evaluate DP acceptance limits</i>

Summary:

- This is an electronic NDA in eCTD format with electronic labeling provided in SPL format. There is a Quality Overall Summary consisting of 65 pages approximately. This NDA is filed as a 505(b)(2) application. Associated INDs are _____ and IND 68,782 (for COPD). A PreNDA meeting took place with this applicant and the expectations from the Agency were laid out in the meeting minutes dated 20-Oct-2005. [NOTE: The drug substance Formoterol Fumarate dihydrate is already approved as a DPI and as a fixed dose combination pMDI.]

b(4)

Drug Substance

- Formoterol fumarate dihydrate is a practically odorless, white to yellowish white powder. It is freely soluble in glacial acetic acid and methanol, slightly soluble in water and ethanol, and practically insoluble in ether. Formoterol is a racemic mixture of (R,R)- and (S,S)-enantiomers, prepared as the fumarate salt in dihydrate form. See structure above.
- Two sources** of formoterol fumarate dihydrate are used for the manufacture of the drug product. _____ LOA dated March 19, 2006) and _____, LOA dated Feb, 14, 2006). Dey claims that the specifications for the drug substance from both sites are the same and that the material from both sites is interchangeable. This needs to be evaluated by the reviewer. Specifications proposed for formoterol fumarate manufactured by Merck Development Center (MDC) are based on the EP monograph, FDA guidance documents, ICH guidelines and test data from three lots of formoterol fumarate manufactured by _____
 Two labs are identified as alternates to Dey labs for microbial testing: _____
- Note that DMF 19202 _____ the synthesis described in the DMF _____

b(4)

b(4)

- The DMF from _____, was reviewed by Dr. Bertha in support of an IND (different dosage form, Inhalation powder) and found adequate. There were comments that were sent out in an information request letter dated 03-Oct-2005. There have been no amendments noted in the DMF addressing these comments, some of which are applicable to the current NDA as well. The reviewer should get in touch with the DMF holder to expedite the responses so that they may be evaluated in light of the current NDA. The synthesis described in the DMF starts from _____ which cannot be considered a starting material. Note that the attributes of polymorphism and particle size distribution may not be applicable to this drug product. b(4)
- Dey Lab's incoming acceptance criteria for drug substance specifications are Description, ID by IR and HPLC, Color (APHA) pH (in water), Water Content, Residue on Ignition, Heavy metals, Assay, Related substances (HPLC), Isomeric Purity (RS, SR diastereomer), Residual Solvents, OVI (USP <467>, method IV), Optical Rotation (USP <761>), and Microbial Limit Test (USP <61>). Note that the drug substance is not very stable in aqueous medium and _____. b(4)
- None of the results for related substances for formoterol obtained from _____ and analyzed by Dey are greater than _____% at release. However, the release COAs from _____ indicates the results for _____, as analyzed by EP method, to be around _____ and _____%. The ambiguity of these methods needs to be clarified.
- The container closure system for the bulk drug substance is referenced to the individual DMFs. Dey claims to store the drug substance in _____.
 _____The material is kept in the original manufacturer package after it has been received. Stability of the drug substance should be evaluated in the DMF. Results for several batches of formoterol fumarate dihydrate, stored at 25/60 conditions (in DMF _____, indicate that the drug substance is quite stable for _____ months without any degradation (Total impurities only _____%). The drug substance appears to be _____ which may have labeling implications. Forced degradation studies need to be evaluated. b(4)

Drug Product

- Formoterol Fumarate Inhalation Solution, 20 mcg/2 mL, is provided in a 2 mL single-use low-density polyethylene (LDPE) vial manufactured by _____ technology. Each vial contains 2 mL of a clear, colorless solution composed of 20 mcg of formoterol (as formoterol fumarate) in an isotonic, sterile aqueous solution containing citric acid, sodium citrate and sodium chloride. Each unit dose vial is over-wrapped in a pre-printed foil laminate pouch and is packaged in cartons of _____ and 60 pouches. b(4)

Table 2.3.P.1.1 Formulation Composition of Formoterol Fumarate Inhalation Solution 20 mcg/2 mL

INGREDIENT	FUNCTION	CONCENTRATION IN DRUG PRODUCT	AMOUNT PER VIAL (2 mL)
Formoterol Fumarate Dihydrate	Active Ingredient	_____ mg/mL*	0.020 mg*
Sodium Chloride, USP	_____	_____	_____
Sodium Citrate _____ e, USP			
Citric Acid / _____ USP			
_____ USP			

* On an anhydrous basis

ONDQA PAL's Initial Quality Assessment
Prasad Peri, Ph.D., Division of Pre-Marketing Assessment 1, Branch 2

- The formulation is available in one strength (10 mcg/mL), although during the preNDA stages Dey was contemplating a concentrated solution (20 mcg/mL-refer to meeting minutes). The pharmaceutical development report provides additional rationale for the use of the excipients at the proposed concentrations. Also note that during Phase 1/2 studies, Dey studied formoterol concentrations ranging from 2.5 to 122 mcg/mL.
- Note that the commercial scale batches are stated to be 100 L. Phase 3 clinical and registrations batches were 10 L. A tabular comparison of the manufacturing process is reproduced below (taken from pharmaceutical development page 5). Clinical batches C062A, C066A, C067A, and C068A were formulated at 10 mcg/mL for use in the pivotal Phase 3 studies.

b(4)

Table 2.3.P.2.2 Comparison of Manufacturing Process: Lab Scale to Commercial Batch Production

	REPRESENTATIVE BATCHES			
	Lab Scale	Phase I/II Clinical	Phase III Clinical and Registration	Proposed Commercial Production Scale
Lot Number	PD1-04-02, p. 100	C054	C086	T644
Manufacturing Site	Dey L.P.	Dey L.P.	Dey L.P.	Dey L.P.
Concentration	10 mcg/mL	10 mcg/mL	10 mcg/mL	10 mcg/mL
Batch Size				
Formulation Vessel				
Mixing				
Filling				
Packaging				

b(4)

Table 9.1.1 Formulation Compositions of FFIS Batches used in Clinical Trials

Ingredients	Batch Number										
	C040	C041	C043	C052	C053	C054	C056	C062A	C066A	C067A	C068A
FF Conc ^a (mcg/mL)											
Sodium Chloride, USP (mg/mL)											
Sodium Citrate (mg/mL), USP											
Citric Acid (mg/mL), USP											

*On an anhydrous basis

b(4)

Table 9.1.2 FFIS Clinical Trial Batch Size, Date of Manufacture, and Use

Batch No.	Phase I/II Clinical Studies							Phase III Clinical Studies			
	C040	C041	C043	C052	C053	C054	C056	C062A ^a	C066A ^a	C067A ^a	C068A ^a
Batch Size (L)											
Date of Manufacture											
Clinical Study No.	DL048 DL052 DL053 DL050	DL048 DL050	DL048 DL050 DL056	DL055 DL057	DL055 DL056 DL057	DL055 DL056 DL057	DL057	DL059 201-065	DL059	DL059	DL059

b(4)

^a C062A, C066A, C067A and C068A are the respective sub-lots of C052, C056, C057 and C058 used for registration stability

- The drug product is manufactured by _____

b(4)

b(4)

b(4)

- When tested using a Pari® LC Plus nebulizer connected to a Proneb® Ultra compressor the mean droplet size distribution results indicate that the D10 is _____ microns, D50 is _____ microns and D90 is _____ microns. The span (D90-D10/D50) was determined to be _____ micron. Using the same nebulizer and connected to an ACI, the mean respirable dose (aerodynamic size between 1.1 and 5.8 mcm) was found to be _____ mcg, equivalent to _____ of label claim. Using the same nebulizer and connected to filter substrate within an emitted dose test chamber, the in vitro delivered dose was found to range between _____ and _____ mcg. The mean delivered dose was found to be 7.3 mcg equivalent to approximately 37% of the label claim under these testing conditions. This should be stated in the label.

b(4)

POSSIBLE CRITICAL ISSUES

- Has all information requested during the IND phases, and at the pre-NDA meetings been included? Yes.

The reviewer needs note the following.

1. Note that the drug product is thermally labile and light sensitive. Results from photostability studies on the non over-wrapped vials indicate a loss of formoterol assay by about 80%. Similarly, when placed at room temperature conditions, the potency is reduced to below 90% within 6 months. Appropriate labeling comments are warranted. Although the applicant claims that the secondary packaging provides sufficient protection from light, no data has been provided. This may be requested in the 74 day letter.
2. For filing the NDA, > months stability data (long term ~C conditions and _____ % RH accelerated conditions) for the drug product was submitted for 7 batches (C066, C067, C068, C086, C087, C088, and C090). Batches C066, C067, C068, C086, C087, and C088 were manufactured using formoterol fumarate dihydrate drug substance obtained from _____ while only batch C090 was manufactured using formoterol fumarate dihydrate drug substance obtained from Merck Development Center (MDC).
3. To support the stability data at room temperature (post dispensing stability study (PDS)), samples from batches stored until 15 months, 18 months, and 21 months were pulled and studied for 3 months. The applicant has really not justified as to why only samples stored

b(4)

beyond 15 months were used in this study as opposed to samples from earlier time points although this may be the worst case scenario.

4. Note that the wording of the Uniformity of dosage units needs to be made more consistent with the previously approved products from Dey LP.
5. It should be clarified why _____ types of _____ are not present in the drug product as leachables as they are listed in other Dey products using the same LDPE vials. [Can we make this comparison with other Dey products?] b(4)

Test for Endotoxins in the Drug product/ _____

_____. Note that there is a big section on the use of _____ and the manufacturing process validation. Since this is a routine manufacturing process for this company, this reviewer feels that no consult needs to be sent in to the Office of Microbiology to evaluate this section. The reviewer and supervisor may consider this at their discretion after reviewing the process validation report. This being a small molecule and not biologically derived, the possibility of endotoxins is minimal. b(4)

• **Weight Loss**

Weight loss is typically reported as loss in weight (mg). Dey reports it as percentage weight loss (from original). This although unusual may be acceptable.

• **Overage in the formulation.**

None proposed.

• **Excipients from Animal Origin.**

None proposed.

• **OVI's in the drug Product**

There are limits for the leachables, (_____) in the drug product. The reviewer should evaluate the proposed limits and send a PT consult if necessary to evaluate the safety of the total daily exposure of each leachable.

• **Manufacturing differences between pilot and commercial scales.**

The primary stability batches for the manufacture of the final blend are _____ the commercial scale. No change in manufacturing process is noted for this simple solution. b(4)

• **GMP status of the drug substance/drug product manufacturing sites.**

Two of the five sites received acceptable status from the Office of Compliance as of this date. Both drug substance sites (Merck Development, India and _____) and the drug product sites are pending a response from the office of compliance. b(4)

• **Safety of imprinting inks.**

None proposed.

• **Degradation products.**

Note that the proposed limits for related substances ' _____ ' is over the ICH Q3B qualification limit. Dey is proposing a total limit of NMT _____ % for ' _____ ' . The safety data regarding the qualification if this impurity should to be evaluated by the pharmacologist. A consult should be sent. **b(4)**

- **Sensitivity of product to moisture and light.**

The drug product is an aqueous solution but light sensitive. See comments above on the photostability of the drug product.

- **Microbial limits in the drug product.**

This is a sterile solution. The sterility assurance process should be evaluated by the microbiologist. A consult will be sent to Jim McVey.

- **Expiration dating period of the drug product.**

Note that the applicant is proposing a 24 months shelf life including a 3 months out of pouch data. So the total in pouch shelf life cannot be more than 21 months. Stability data need to be evaluated to justify this.

- **Bulk Drug Product Stability Packaging Data and Protocol**

None proposed.

- **Preliminary comments on labeling.**

None identified.

Comments for the 74 day letter:

You claim that the drug product in the secondary packaging configuration is stable. Provide a reference to the photostability data for the over wrapped drug product.

Collect and provide post dispensing stability data for vials that were opened prior to 15 months. Update the NDA with this data as soon as possible. If these are considered not representative of what the patient might do, please provide a justification for this.

The post dispensing stability data results for the attribute "Weight Loss" has not been provided. This needs to be justified.

2 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Supporting NDA or IND: None.

DMF:

DMF	TYPE	HOLDER	ITEM REFERENCED	COMMENTS
19202	II	Merck Devp. Center	Formoterol Fumarate Dihydrate	
_____	II	_____	_____	
_____	III	_____	_____	LOA is provided. Although adequate , an IR letter was issued to the company in 2001. It is not clear why the DMF holder did not respond to the comments. A message was left for the DMF holder to respond to this. The Reviewer needs to follow up on this only for documentation purposes.
_____	III	_____	_____	Although the same materials are used in the NDA for _____ and _____, the latest amendment dated 4-3-2003 not 11-21-2005 as stated in the LOA. A quick cursory chemistry review of the amendment may be needed

b(4)

ONDQA PAL's Initial Quality Assessment
 Prasad Peri, Ph.D., Division of Pre-Marketing Assessment 1, Branch 2

Note all requests for EES were submitted on 17/18-July-2006 by Dr. Scott Goldie.

**Formoterol Fumarate Inhalation Solution, 20 mcg/2 mL
 Drug Establishment Information**

Drug/Component	Company Name and Address	Contact Name and Number	Activities	Reference	Ready For Inspection?
Formoterol Fumarate Inhalation Solution, 20 mcg/2 mL	Dey, L.P. 2751 Napa Valley Corporate Drive Napa, CA 94558	Michelle A. Carpenter, JD VP, Regulatory Affairs and Clinical Development (707) 224-3200 x 4750	NDA Sponsor Drug product manufacturing, packaging, Release and Stability Testing	Registration Establishment Number/ CFN 2938970	Yes
Formoterol Fumarate Dihydrate	Merck Development Center (MDC) 1A/2, M.I.D.C Industrial Estate Taloja, Parvel INDIA	Dr. K. Walavalkar DGM – QA and Regulatory Affairs 91-22-27402900	Drug substance manufacture, release and stability testing	Registration Establishment Number: Type II DMF Number: 19202	Yes
	King & Spalding 1700 Pennsylvania Ave. N.W. Washington, DC 20006	Christina M. Markus (202) 626-2926	US Agent for Merck Development Center	N/A	N/A
Formoterol Fumarate Dihydrate	_____		Drug substance manufacture Release and stability testing	Registration Establishment Number: Type II DMF Number: _____	Yes
	_____			N/A	N/A

b(4)

Drug/Component	Company Name and Address	Contact Name and Number	Activities	Reference	Ready For Inspection?
Low Density Polyethylene (LDPE)	_____			Type III DMF Number: _____	Yes
	_____			Type III DMF Number: _____	Yes

b(4)

CHEMISTRY NDA FILEABILITY CHECKLIST

NDA Number: 22-007 Applicant: Dey LP Stamp Date: 29-June-2006
Drug Name: Formoterol Fumarate Inhalation solution

IS THE CMC SECTION OF APPLICATION FILEABLE? Yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		
6	Has an environmental assessment report or categorical exclusion been provided?	X		
7	Does the section contain controls for the drug substance?	X		
8	Does the section contain controls for the drug product?	X		
9	Have stability data and analysis been provided to support the requested expiration date?	X		
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?		X	Note that during the EOP2 meeting there was mention of a concentrated solution (20. mcg/0.5 mL). This is not provided in this NDA.
14	Is there a Methods Validation package?	X		
15	Is a separate microbiological section included?		X	Sterile solution. Aseptically filled. Sterility assurance program should be evaluated by a microbiologist.

Draft CMC comments for the 74 day letter

Comments for the 74 day letter:

You claim that the drug product in the secondary packaging configuration is stable. Provide a reference to the photostability data for the over wrapped drug product.

Collect and provide post dispensing stability data for vials that were opened prior to 15 months. Update the NDA with this data as soon as possible. If these are considered not representative of what the patient might do, please provide a justification for this.

The post dispensing stability data results for the attribute "Weight Loss" has not been provided. This needs to be justified.

APPEARS THIS WAY ON ORIGINAL

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

/s/

Prasad Peri
8/1/2006 10:50:30 AM
CHEMIST

Blair Fraser
8/1/2006 11:13:00 AM
CHEMIST

26 Page(s) Withheld

 Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Withheld Track Number: Pharm/Tox- 1

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

/s/

Blair Fraser
8/10/2006 01:15:31 PM

4 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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

/s/

Timothy Robison
2/5/2007 04:21:05 PM
PHARMACOLOGIST

Joseph Sun
2/6/2007 04:25:16 PM
PHARMACOLOGIST
I concur.