CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-592

CHEMISTRY REVIEW(S)

FORADIL CERTIHALER
(FORMOTEROL FUMARATE)
INHALATION POWDER
NDA 21-592

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Indication: long-term, twice-daily (morning and evening) administration in the maintenance treatment of asthma and in the prevention of bronchospasm in adults and children 5 years of age and older with reversible obstructive airway disease

Presentation: Single strength of 10 mcg of formoterol fumarate, metered per actuation to deliver an emitted dose of 8.5 mcg

Strength is contained in a multi-dose, dry powder inhaler which is designed to deliver 60 doses of the formulation and is fitted with a decrementing counter. No additional protective packaging is required.

Additionally, the physician sample is provided as a 16 dose presentation which is identical to the 60 dose device but instead is equipped with a lock-out and decrementing counter initially set at 15.

EER Status: **Acceptable** 22-NOV-2006

Consults: **EA:** Categorical exclusion granted under 21 CFR §25.31(b).
Biometrics: No consult requested.
Methods Validation: Applicant agrees to submit MV package within 3 months of the approval date of the application.

Original Submission: 17-DEC-2002

Re-submissions: 17-MAR-2003
24-JUN-2004
15-JUN-2006

Post-Approval Agreements:

Novartis has agreed to the following in the 04-OCT-2004, amendment:

1. You will submit a prior approval supplement post-approval to revise, if feasible, the acceptance criteria for the aerodynamic particle size distribution (APSD) by [redacted] once [redacted] consecutive production scale drug product batches are manufactured with well-controlled lactose and tested with the optimized procedures (i.e., suitable absolute and vacuum ramp profile, environmental controls, optimized device equilibration and handling). You will avoid proposing permissive acceptance criteria to encompass all data for all [redacted] stage groupings for all batches produced thus far, since this will **not be in the best interest of quality control. You will establish the "linkage" of** production scale batch APSD to that for the clinical/primary stability batches focusing on the groups expected to be most clinically relevant (e.g., S2-S4). b(4)

2. You will continue to investigate what measured parameters of the lactose can be used to detect changes that will impact on the resultant aerodynamic particle size distribution of the drug product. Once identified, these can be implemented as controls for acceptance of incoming lactose.

3. You will continue to monitor the levels of amorphous content of the lactose excipient and consider the introduction of a mandatory storage period prior to use in formulation and/or a tightening of the specification acceptance criterion.

4. You will finalize the impurities acceptance criteria for the lactose once [redacted] lactose batches are manufactured using [redacted] final process to produce lactose for your drug product. b(4)

5. You will establish final acceptance criteria for the routine extractables for the critical components of the drug product device once the extractables results from [redacted] batches are obtained. b(4)

6. The following agreements pertain to the control of foreign particulates in the drug product components and subcomponents.

a. You will reevaluate the acceptance criteria applied at release for foreign particulates in filled reservoirs of the drug product and tighten these, if appropriate, to reflect the data from the first [redacted] consecutive production batches. b(4)

b. You will reevaluate the acceptance criteria applied for acceptance of the levels of foreign particulates in the lactose excipient and the empty reservoirs and tighten these, if appropriate, to reflect the data from the first [redacted] consecutive batches, respectively, received for production batches of the drug product. b(4)

c. You will undertake every reasonable effort to decrease the levels of foreign particulates that may emanate from the drug product during patient usage, and agree that the final acceptance criteria for drug product

components (i.e., empty reservoirs, lactose) and subcomponents (i.e., formulation-filled reservoirs) will not be widened from the interim levels proposed in the June 24, 2004, amendment.

7. You agree to provide the updated Mg stearate testing monograph including the **revision tightening the specific surface area specification to** [redacted] m^2/g. b(4)

8. You agree to provide a methods validation package as outlined in comment 6j of the October 17, 2003, letter within 3 months following the approval of the application.

Drug Substance:

Formoterol fumarate is a long-acting β_2-adrenergic agonist (LABA), is a racemic mixture, and has the chemical name (±)-2-hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]-amino]ethyl]formanilide fumarate dihydrate. It is a white to yellowish powder with a molecular weight of 840.9 Da and the empirical formula of $(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot 2H_2O$. Formoterol free-base has a molecular weight of 344.41 Da. Further information about formoterol fumarate appears in the approved application NDA 20-831 for Foradil Aerolizer.

Conclusion: Drug substance is acceptable.

Drug Product:

The drug product is a "device-metered" dry powder inhaler which is designed to deliver 60 inhalations of the formulation and includes a decrementing counter. The formulation contains [redacted] % w/w formoterol fumarate with lactose monohydrate as the [redacted] excipient and [redacted] % w/w magnesium stearate as a [redacted] b(4)

The airflow resistance of the **device is** [redacted] **cm** $H_2O^{1/2}$/L/min (medium resistance) and is specified to actuate with a flow of [redacted] L/min (termed actuation flow rate or AFR). The dose content uniformity (DCU) data indicate that drug product units do not meet the [redacted] % LC mean acceptance criteria at a lower end flow rate of 30L/min at the beginning of unit actuations. b(4)

Drug product performance parameters, which are key measures of quality, are the DCU through-life and the aerodynamic particle size distribution (APSD).

Minor device "improvements" were made when proceeding from the clinical trial devices prepared with [redacted], to the commercial devices prepared with [redacted] tools. b(4)

Adequate stability data were provided to support a **24 month expiration dating period** when stored at 25°C with excursions permitted from 15 to 30°C. The labeling also cautions to protect the product from heat and moisture.

Conclusion: Drug product is satisfactory.

Additional Items:

All associated Drug Master Files (DMFs) are acceptable or the pertinent information has been adequately provided in the application.

The package insert, container labels, and carton labels are acceptable.

Overall Conclusion:

From a CMC perspective, the application is recommended for **approval**.

Blair A. Fraser, Ph.D.
Branch Chief, Branch II
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
11/29/2006 09:00:45 AM
CHEMIST

NDA 21-592
Chemistry Review #6

Foradil® Certihaler™
(formoterol fumarate inhalation powder)

Novartis Pharmaceuticals Corporation

Craig M. Bertha, Ph.D.
Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-592

2. REVIEW #: 6

3. REVIEW DATE: 05-JUL-2006

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	17-DEC-2002
Amendment (AC)	17-MAR-2003
Amendment (BZ)[1]	01-DEC-2003
Amendment	15-JUL-2003
Amendment	29-AUG-2003
Amendment (AZ)	24-JUN-2004
Amendment (BC)	04-OCT-2004
Amendment (BC)[1]	22-NOV-2004
Original Submission[2]	17-DEC-2002
Correspondence	02-FEB-2006
Correspondence	01-MAR-2006

[1]Submission is a response to the CMC discipline review (DR) telephone facsimile letter of 17-NOV-2004.
[2]Carton and container labels only.

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (BC)	29-MAR-2006
Amendment (BL)	30-MAR-2006
Amendment (AZ)	15-JUN-2006 (assigned 21-JUN-2006)

7. NAME & ADDRESS OF APPLICANT:

Name: Novartis Pharmaceuticals Corporation

Chemistry Review Data Sheet

Address:	One Health Plaza East Hanover, New Jersey 07936-1080
Representative:	Ann Shea, Associate Director Drug Regulatory Affairs
Telephone:	862-778-4567

8. DRUG PRODUCT NAME/CODE/TYPE:

a) **Proprietary Name: Foradil® Certihaler™**
b) Non-Proprietary Name (USAN): formoterol fumarate inhalation powder
c) Code Name/# (OGD only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: β_2-adrenergic bronchodilator for prevention and maintenance treatment of asthma

11. DOSAGE FORM: Inhalation Powder

12. STRENGTH/POTENCY: 5.6 mg (per actuation) of formulation contains 10 mcg (metered dose of formoterol fumarate), 8.5 mcg target emitted dose equivalent to 8.2 mcg of formoterol base; reservoir target fill of 560 mg formulation of [redacted] % w/w formoterol fumarate concentration with lactose and [redacted] Mg stearate, [redacted] mg formoterol fumarate per reservoir b(4)

13. ROUTE OF ADMINISTRATION: oral inhalation

14. Rx/OTC DISPENSED: X Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____**SPOTS product – Form Completed**

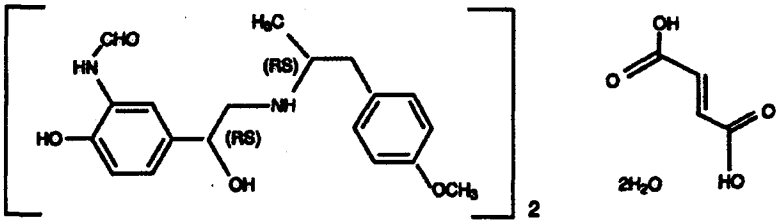
__X__Not a SPOTS product

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

(±)-2-hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]-amino]ethyl]formanilide fumarate dihydrate

$(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot 2H_2O$

Chemistry Review Data Sheet



MW = 840.9
MW = 344.414 for formoterol free-base

17. RELATED/SUPPORTING DOCUMENTS:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
[redacted]				1	Adequate	7/23/04	See p. 51 in CR#1, See p. 37 in CR#2
				1	Adequate	7/5/06	See p. 96 in CR#1, See p. 102 in CR#2 See p. 10 of CR#6.
				1	Adequate	10/25/04	See p. 45 in CR#1, See p. 18 in CR#2 See p. 13 in CR#3

b(4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 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")

[2] Adequate, Inadequate, or N/A (There are enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
N20-831	Novartis Pharmaceuticals Corporation	Drug Substance	Adequate	08-Dec-2000	DS for capsule for inhalation (pre-metered) **drug product using Aerolizer™ device** (approved 2/16/01)

Chemistry Review Data Sheet

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	60,254	Novartis	Original IND for the current drug product

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				Consult not needed. See evaluation on p. 113 of CR#2.
EES	site inspections	22-JUN-2006	Pending	
Pharm/Tox				N/A
Biopharm				
LNC				N/A
Methods Validation				To be forwarded once specifications and methods finalized. See attached list of agreements.
OPDRA	device trademark	16-JAN-2003	Acceptable/Tia Harper-Valazquez	For device trademark "Certihaler™"
EA				N/A, <1 ppb expected at aquatic point of entry (p. 2, section 1-5)
Microbiology				Not needed. See evaluation on p. 86 of CR#2.

The Chemistry Review for NDA 21-592

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for **approval**, from a CMC perspective, pending an acceptable recommendation from the Office of Compliance.

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

The current CMC agreements are collated at the end of CR#4 and have been reproduced in the attached letter. Prior to approval, the PM should send the applicant a copy of these agreements to verify concurrence.

II. Summary of Chemistry Assessments

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

The drug product is a multi-dose dry powder inhaler which is designed to deliver 60 inhalations of the formulation for BID usage. The drug substance is a dihydrate of formoterol fumarate, which is already approved for inhalation with the Foradil Aerolizer Inhalation Powder product of N20-831. It has the molecular formula $(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot 2H_2O$ and a molecular weight of 840.9. The drug product is indicated for long-term maintenance treatment of asthma and in the prevention of bronchospasm in adults and children 5 years and older with reversible obstructive **airway disease,** [redacted] **. The product is a "device-metered"** dry powder inhaler with lactose monohydrate as the [redacted] t excipient. The formulation b(4)
also includes a [redacted] amount of magnesium stearate ([redacted] w/w), which is claimed to aid in [redacted] . The device has a **counter which counts down from "60" for each** individual actuation. Counting takes place after the dose is obtained and the mouthpiece cover is **put back into place. After reaching "00" the d**evice will allow the patient to receive one more **actuation. After this the counter will read "999"** and the device will lock preventing further use. If, in the future, the unit is to be approved for *pro re nata* use, the lockout of the device may be an issue of concern. A physician sample vari**ant (termed "003") is identical to the 60 count** device but the lock-out occurs after 16 actuations have been used (counter set at 15 initially, see 3.2.P.8.3.2.3).

The airflow resistance of the **device is** [redacted] **cm** $H_2O^{1/2}$/L/min ([redacted] resistance) and b(4)
is specified to actuate with a flow of [redacted] L/min (termed actuation flow rate or AFR) i.e., a
metered dose will not be emitted unless the AFR is met. The mean AFR being observed for devices is ~30 L/min. Usage of the device leads to about a 5 L/min increase, on average, in the

AFR, which is thought to be due to [redacted] Individual AFRs for b(4)
product with devices prepared with [redacted] **tools ranged consistently from 30 – 45** L/min in an *in vitro* study examining the increase with usage (see p. 17 of the 29-AUG-2003, amendment and p. 12 of CR#2). A 5 L/min increase in the AFR was not expected to be detectable by patients as they typically generated flow rates well above 40 L/min (see p. 57 of CR#2). The dose content uniformity (DCU) data indicate that drug product units do not meet the [redacted] % LC mean acceptance criteria at a lower end flow rate of 30L/min at the beginning of unit actuations (see study on effect of flow rate on product performance on p. 18 in CR#1).

The device does not utilize any additional protective packaging (e.g., foil laminate overwrap) nor does it contain an internal desiccant. Under Agency direction the applicant undertook a stability study with protective foil overwrap in place for the DP. In summary, data did not support the need for a foil laminate overwrap (for results and evaluation see p. 121 of CR#2). Also refer to the response to comment 4c in CR#3 regarding modification of the device counter components.

Drug product performance parameters which are key measures of quality are the DCU through-life and the aerodynamic particle size distribution (APSD).

Minor device "improvements" were made when proceeding from the clinical trial devices prepared with [redacted], to the commercial devices prepared with [redacted] b(4)
[redacted] tools. For a comparison of performance data from commercial versus the clinical product see the response and evaluation to comments 7d (DCU) and 7g (APSD) in CR#2. Due to a recall of the product from the German and Swiss marketplace for an overdosing problem, major device modifications have been made. The details of these revisions and an evaluation of the relevant *in vitro* behavior of the drug product are covered in the current review #6.

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

The drug product is designed to deliver 8.5 mcg of formoterol fumarate (as the dihydrate) with each actuation in a formulation of lactose with magnesium stearate. The patient is instructed to take one inhalation from the device twice a day approximately 12 hours apart (i.e., 17 mcg daily **dose). The patient's instructions for use in** the labeling recommend that the drug product **mouthpiece be cleaned with a "dry cleaning method" on a weekly basis. The data presented in** response to comment 9c of the 17-OCT-2003, AE letter supports this cleaning recommendation.

Currently the applicant is proposing a **24 month expiration dating period**, which is considered to be adequate based on the data that have been provided (see p. 113 of CR#2 for evaluation of response to comment 10d).

The current recommended storage conditions are 25°C with excursions permitted from 15 to 30°C. The labeling also cautions to protect the product from heat and moisture. The product is not proposed to have any additional protective packaging (e.g., foil overwrap) nor do the data support the need for such packaging (see p. 121 of CR#2).

C. Basis for Approvability or Not-Approval Recommendation

N/A

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Craig M. Bertha, Ph.D., Review Chemist
ONDQA

C. CC Block

cc:
Orig. NDA 21-592
OND/DPAP/Division File
ONDQA/DIV1/CBertha/07/05/06
ONDQA/DIV1/PPeri
ONDQA/DIV1/BFraser
OND/DPAP/AGreen
OND/DPAP/SBarnes

R/D Init. by: BFraser_____

Filename and Location: c:\data\mydocuments\reviews etc\NDA\21592\06-06-15_rev.doc

16 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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

/s/

Craig Bertha
7/6/2006 08:18:44 AM
CHEMIST

AZ amendment on EDR

Blair Fraser
7/7/2006 06:32:15 AM
CHEMIST

NDA 21-592
Chemistry Review #5

Foradil® Certihaler™
(formoterol fumarate inhalation powder)

Novartis Pharmaceuticals Corporation

Craig M. Bertha, Ph.D.
Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-592

2. REVIEW #: 5

3. REVIEW DATE: 09-MAR-2006

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	17-DEC-2002
Amendment AC	17-MAR-2003
Amendment BZ[1]	01-DEC-2003
Amendment	15-JUL-2003
Amendment	29-AUG-2003
Amendment (AZ)	24-JUN-2004
Amendment BC	04-OCT-2004
Amendment BC[1]	22-NOV-2004
Original Submission[2]	17-DEC-2002

[1]Submission is a response to the CMC discipline review (DR) telephone facsimile letter of 17-NOV-2004.
[2]Carton and container labels only.

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (AZ)	10-OCT-2005
Correspondence	02-FEB-2006
Correspondence	01-MAR-2006

7. NAME & ADDRESS OF APPLICANT:

Name: Novartis Pharmaceuticals Corporation

Address: One Health Plaza
East Hanover, New Jersey 07936-1080

Chemistry Review Data Sheet

Representative: Ann Shea, Associate Director Drug Regulatory Affairs

Telephone: 862-778-4567

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Foradil® Certihaler™
b) Non-Proprietary Name (USAN): formoterol fumarate inhalation powder
c) Code Name/# (OGD only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: β_2-adrenergic bronchodilator for prevention and maintenance treatment of asthma

11. DOSAGE FORM: Inhalation Powder

12. STRENGTH/POTENCY: 5.6 mg (per actuation) of formulation contains 10 mcg (metered dose of formoterol fumarate), 8.5 mcg target emitted dose equivalent to 8.2 mcg of formoterol base; reservoir target fill of 560 mg formulation of [redacted] w/w formoterol fumarate concentration with lactose and [redacted] Mg stearate, [redacted] ng formoterol fumarate per reservoir b(4)

13. ROUTE OF ADMINISTRATION: oral inhalation

14. Rx/OTC DISPENSED: X Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

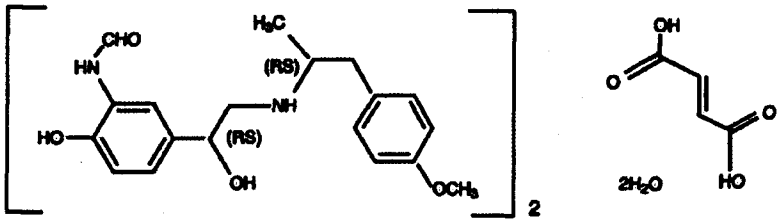
__X__Not a SPOTS product

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

(±)-2-hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]-amino]ethyl]formanilide fumarate dihydrate

$(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot 2H_2O$

Chemistry Review Data Sheet



MW = 840.9
MW = 344.414 for formoterol free-base

17. RELATED/SUPPORTING DOCUMENTS:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
				1	Adequate	7/23/04	See p. 51 in CR#1, See p. 37 in CR#2
				1	Adequate	7/21/04	See p. 96 in CR#1, See p. 102 in CR#2
				1	Adequate	10/25/04	See p. 45 in CR#1, See p. 18 in CR#2 See p. 13 in CR#3

b(4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
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5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There are enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
N20-831	Novartis Pharmaceuticals Corporation	Drug Substance	Adequate	08-Dec-2000	DS for capsule for inhalation (pre-metered) drug product using Aerolizer™ device (approved 2/16/01)

Chemistry Review Data Sheet

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	60,254	Novartis	Original IND for the current drug product

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				Consult not needed. See evaluation on p. 113 of CR#2.
EES	site inspections	21-JAN-2003	Acceptable	OC recommendation of 13-JAN-2004
Pharm/Tox				N/A
Biopharm				
LNC				N/A
Methods Validation				To be forwarded once specifications and methods finalized. See attached list of agreements.
OPDRA	device trademark	16-JAN-2003	Acceptable/Tia Harper-Valazquez	For device trademark "Certihaler™"
EA				N/A, <1 ppb expected at aquatic point of entry (p. 2, section 1-5)
Microbiology				Not needed. See evaluation on p. 86 of CR#2.

The Chemistry Review for NDA 21-592

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is considered to be **approvable (AE)** from a CMC perspective. The PM should include the comment in the attached draft letter in the action letter.

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

The current CMC agreements are collated at the end of CR#4. Prior to approval the applicant should be sent a copy of these to verify their concurrence.

II. Summary of Chemistry Assessments

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

The drug product is a multi-dose dry powder inhaler which is designed to deliver 60 inhalations of the formulation for BID usage. The drug substance is a dihydrate of formoterol fumarate, which is already approved for inhalation with the Foradil Aerolizer Inhalation Powder product of N20-831. It has the molecular formula $(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot 2H_2O$ and a molecular weight of 840.9. The drug product is indicated for long-term maintenance treatment of asthma and in the prevention of bronchospasm in adults and children 5 years and older with reversible obstructive airway disease, [redacted] The product is a "device-metered" dry powder inhaler with lactose monohydrate as the [redacted] excipient. The formulation also includes a [redacted] amount of magnesium stearate ([redacted] w/w), which is claimed to aid in [redacted] The device has a counter which counts down from "60" for each individual actuation. Counting takes place after the dose is obtained and the mouthpiece cover is put back into place. After reaching "00" the device will allow the patient to receive one more actuation. After this the counter will read "999" and the device will lock preventing further use. If, in the future, the unit is to be approved for *pro re nata* use, the lockout of the device may be an issue of concern. A physician sample variant (termed "003") is identical to the 60 count device but the lock-out occurs after 16 actuations have been used (counter set at 15 initially, see 3.2.P.8.3.2.3). b(4)

The airflow resistance of the device is [redacted] cm $H_2O^{1/2}$/L/min [redacted] resistance) and is specified to actuate with a flow of [redacted] L/min (termed actuation flow rate or AFR) i.e., a metered dose will not be emitted unless the AFR is met. The mean AFR being observed for devices manufactured with [redacted] tools is 25 L/min. Usage of the device leads to b(4)

about a 5 L/min increase, on average, in the AFR, which is due to increased [redacted]

Individual AFRs for product with devices prepared with [redacted] tools ranged consistently from 30 – 45 L/min in an *in vitro* study examining the increase with usage (see p. 17 of the 29-AUG-2003, amendment and p. 12 of CR#2). A 5 L/min increase in the AFR was not expected to be detectable by patients as they typically generated flow rates well above 40 L/min (see p. 57 of CR#2). The dose content uniformity (DCU) data indicate that drug product units do not meet the [redacted] % LC mean acceptance criteria at a lower end flow rate of 30L/min at the beginning of unit actuations (see study on effect of flow rate on product performance on p. 18 in CR#1). b(4)

The device does not utilize any additional protective packaging (e.g., foil laminate overwrap) nor does it contain an internal desiccant. Under Agency direction the applicant undertook a stability study with protective foil overwrap in place for the DP. In summary, data did not support the need for a foil laminate overwrap (for results and evaluation see p. 121 of CR#2). Also refer to the response to comment 4c in CR#3 regarding modification of the device counter components.

Drug product performance parameters which are key measures of quality are the DCU through-life and the aerodynamic particle size distribution (APSD).

Minor device "improvements" were made when proceeding from the clinical trial devices prepared with [redacted] to the commercial devices prepared with [redacted] tools. For a comparison of performance data from commercial versus the clinical product see the response and evaluation to comments 7d (DCU) and 7g (APSD) in CR#2. b(4)

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

The drug product is designed to deliver 8.5 mcg of formoterol fumarate (as the dihydrate) with each actuation in a formulation of lactose with magnesium stearate. The patient is instructed to take one inhalation from the device twice a day approximately 12 hours apart (i.e., 17 mcg daily dose). The patient's instructions for use in the labeling recommend that the drug product mouthpiece be cleaned with a "dry cleaning method" on a weekly basis. The data presented in response to comment 9c of the 17-OCT-2003, AE letter supports this cleaning recommendation.

Currently the applicant is proposing a **24 month expiration dating period**, which is considered to be adequate based on the data that have been provided (see p. 113 of CR#2 for evaluation of response to comment 10d).

The current recommended storage conditions are to store at 25°C with excursions permitted from 15 to 30°C. The labeling also cautions to protect the product from heat and moisture. The product is not proposed to have any additional protective packaging (e.g., foil overwrap) nor do the data support the need for such packaging (see p. 121 of CR#2).

C. Basis for Approvability or Not-Approval Recommendation

Executive Summary Section

The applicant had been considered ready for approval from a CMC perspective after the last review #4. However, since that time there have been two correspondences dated 02-FEB-2006, and 01-MAR-2006, that have resulted in a change in the recommendation to **approvable (AE)**. These two correspondences are the subject of the current review. These correspondences provide information on the recent recall of the drug product from both the German and Swiss markets as a result of 5 cases of suspected overdose.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Craig M. Bertha, Ph.D., Review Chemist
ONDQA

C. CC Block

cc:
Orig. NDA 21-592
OND/DPAP/Division File
ONDQA/DIV1/CBertha/03/09/06
ONDQA/DIV1/PPeri
ONDQA/DIV1/BFraser
OND/DPAP/AGreen
OND/DPAP/SBarnes

R/D Init. by: BFraser_____

Filename and Location: c:\data\mydocuments\reviews etc\NDA\21592\06-03-01_rev.doc

5 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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

/s/

Craig Bertha
3/9/2006 08:51:04 AM
CHEMIST

Blair Fraser
3/9/2006 09:44:27 AM
CHEMIST

NDA 21-592
Chemistry Review #4

Foradil® Certihaler™
(formoterol fumarate inhalation powder)

Novartis Pharmaceuticals Corporation

Craig M. Bertha, Ph.D.
Division of Pulmonary and Allergy Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-592

2. REVIEW #: 4

3. REVIEW DATE: 30-NOV-2004

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	17-DEC-2002
Amendment AC	17-MAR-2003
Amendment BZ[1]	01-DEC-2003
Amendment	15-JUL-2003
Amendment	29-AUG-2003
Amendment (AZ)	24-JUN-2004
Amendment BC	04-OCT-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment BC[1]	22-NOV-2004
Original Submission[2]	17-DEC-2002

[1]Submission is a response to the CMC discipline review (DR) telephone facsimile letter of 17-NOV-2004. The Division Goal date and planned date for action is 10-DEC-2004.
[2]Carton and container labels only.

7. NAME & ADDRESS OF APPLICANT:

Chemistry Review Data Sheet

Name:	Novartis Pharmaceuticals Corporation
Address:	One Health Plaza East Hanover, New Jersey 07936-1080
Representative:	Orin Tempkin, Ph.D., Global Regulatory CMC Representative
Telephone:	862-778-6949

8. DRUG PRODUCT NAME/CODE/TYPE:

a) **Proprietary Name: Foradil® Certihaler™**
b) Non-Proprietary Name (USAN): formoterol fumarate inhalation powder
c) Code Name/# (OGD only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: β_2-adrenergic bronchodilator for prevention and maintenance treatment of asthma

11. DOSAGE FORM: Inhalation Powder

12. STRENGTH/POTENCY: 5.6 mg (per actuation) of formulation contains 10 mcg (metered dose of formoterol fumarate), 8.5 mcg target emitted dose equivalent to 8.2 mcg of formoterol base; reservoir target fill of 560 mg formulation of [redacted] % w/w formoterol fumarate concentration with lactose and [redacted] Mg stearate, [redacted] mg formoterol fumarate per reservoir b(4)

13. ROUTE OF ADMINISTRATION: oral inhalation

14. Rx/OTC DISPENSED: X Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____**SPOTS product – Form Completed**

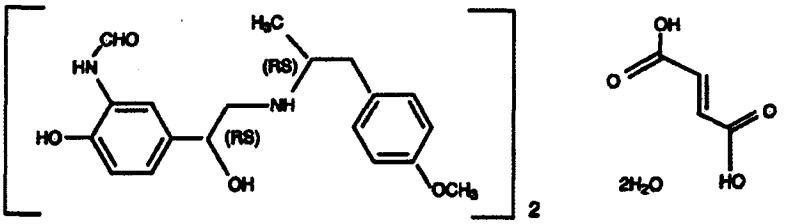
___X___Not a SPOTS product

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

(±)-2-hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]-amino]ethyl]formanilide fumarate dihydrate

Chemistry Review Data Sheet

$(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot 2H_2O$



MW = 840.9
MW = 344.414 for formoterol free-base

17. RELATED/SUPPORTING DOCUMENTS:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
[redacted]				1	Adequate	7/23/04	See p. 51 in CR#1, See p. 37 in CR#2
				1	Adequate	7/21/04	See p. 96 in CR#1, See p. 102 in CR#2
				1	Adequate	10/25/04	See p. 45 in CR#1, See p. 18 in CR#2 See p. 13 in CR#3

b(4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 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")

[2] Adequate, Inadequate, or N/A (There are enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
N20-831	Novartis Pharmaceuticals Corporation	Drug Substance	Adequate	08-Dec-2000	DS for capsule for inhalation (pre-metered) drug product using Aerolizer™ device (approved 2/16/01)

Chemistry Review Data Sheet

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	60,254	Novartis	Original IND for the current drug product

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				Consult not needed. See evaluation on p. 113 of CR#2.
EES	site inspections	21-JAN-2003	Acceptable	OC recommendation of 13-JAN-2004
Pharm/Tox				N/A
Biopharm				
LNC				N/A
Methods Validation				To be forwarded once specifications and methods finalized. See attached list of agreements.
OPDRA	device trademark	16-JAN-2003	Pending	For device trademark "Certihaler™"
EA				N/A, <1 ppb expected at aquatic point of entry (p. 2, section 1-5)
Microbiology				Not needed. See evaluation on p. 86 of CR#2.

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-592

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended to be approved (**AP**) from a CMC perspective. The PM should forward the labeling comment in the attached draft letter to the applicant in the action letter.

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

The current CMC agreements are collated at the end of this review. Prior to approval the applicant should be sent a copy of these to verify their concurrence.

II. Summary of Chemistry Assessments

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

The drug product is a multi-dose dry powder inhaler which is designed to deliver 60 actuations **or "shots" of the formulation for BID usage. It** is indicated for long-term maintenance treatment of asthma and in the prevention of bronchospasm in adults and children 5 years and older with reversible obstructive airway disease, [redacted] The product b(4)
is a "device-metered" dry powder inhaler with lactose monohydrate as the [redacted] excipient. The formulation also includes a [redacted] amount of magnesium stearate ([redacted] w/w), which is claimed to aid in [redacted] The device has a counter which counts down **from "60" for each individual actuation. Counting** takes place after the dose is obtained and the mouthpiece cover is put back into place. After **reaching "00" the device will allow the patient to** receive one more actuation. After this the **counter will read "999" and the device will lock preventing further use. If, in the future, the unit is to be approved for "as-needed" (PRN) use, the** lockout of the device may be an issue of concern. **A physician sample variant (termed "003") is** identical to the 60 count device but the lock-out occurs after 16 actuations have been used (counter set at 15 initially, see 3.2.P.8.3.2.3).

The airflow resistance of the device is ([redacted] **cm** $H_2O^{1/2}$/L/min ([redacted] resistance) and b(4)
is specified to actuate with a flow of [redacted] L/min (termed actuation flow rate or AFR) i.e., a metered dose will not be emitted unless the AFR is met. The mean AFR being observed for devices manufactured with [redacted] tools is 25 L/min. Usage of the device leads to about a 5 L/min increase, on average, in the AFR, which is due to [redacted] Individual AFRs for product with devices prepared with [redacted] **tools ranged consistently from 30 – 45 L/min in** b(4)

an *in vitro* study examining the increase with usage (see p. 17 of the 29-AUG-2003, amendment and p. 12 of CR#2). A 5 L/min increase in the AFR was not expected to be detectable by patients as they typically generated flow rates well above 40 L/min (see p. 57 of CR#2). The dose content uniformity (DCU) data indicate that drug product units do not meet the [redacted] LC mean acceptance criteria at a lower end flow rate of 30L/min at the beginning of unit actuations (see study on effect of flow rate on product performance on p. 18 in CR#1). b(4)

The device does not utilize any additional protective packaging (e.g., foil laminate overwrap) nor does it contain an internal desiccant. Under Agency direction the applicant undertook a stability study with protective foil overwrap in place for the DP. In summary, data did not support the use of foil laminate overwrap (for results and evaluation see p. 121 of CR#2). Also refer to the response to comment 4c in CR#3 regarding modification of the device counter components.

Drug product performance parameters which are key measures of quality are the DCU through-life and the aerodynamic particle size distribution (APSD).

Minor device "improvements" were made when proceeding from the clinical trial devices prepared with [redacted] to the commercial devices prepared with [redacted] tools. For a comparison of performance data from commercial versus the clinical product see the response and evaluation to comments 7d (DCU) and 7g (APSD) in CR#2.

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

The drug product is designed to deliver 8.5 mcg of formoterol fumarate (as the dihydrate) with each actuation in a formulation of lactose with magnesium stearate. The patient is instructed to take one inhalation from the device twice a day approximately 12 hours apart (i.e., 17 mcg daily **dose). The patient's instructions for use in** the labeling recommend that the drug product **mouthpiece be cleaned with a "dry cleaning method"** on a weekly basis. The data presented in response to comment 9c of the 17-OCT-2003, AE letter supports this cleaning recommendation.

Currently the applicant is proposing a **24 month expiration dating period**, which is considered to be adequate based on the data that have been provided (see p. 113 of CR#2 for evaluation of response to comment 10d).

The current recommended storage conditions are to store at 25°C with excursions permitted from 15 to 30°C. The labeling also cautions to protect the product from heat and moisture. The product is not proposed to have any additional protective packaging (e.g., foil overwrap) nor do the data support the need for such packaging (see p. 121 of CR#2).

C. Basis for Approvability or Not-Approval Recommendation

N/A

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Craig M. Bertha, Ph.D., Review Chemist
HFD-570/820

C. CC Block

cc:
Orig. NDA 21-592
HFD-570/Division File
HFD-570/CBertha/11/30/04
HFD-570/RLostritto
HFD-570/AGreen
HFD-570/SBarnes

R/D Init. by: RLosttrito_____

Filename and Location: c:\data\mydocuments\reviews etc\NDA\21592\04-11-22_rev.doc

APPEARS THIS WAY
ON ORIGINAL

5 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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

/s/

Craig Bertha
12/7/04 11:12:18 AM
CHEMIST

Richard Lostritto
12/7/04 01:58:21 PM
CHEMIST

NDA 21-592
Chemistry Review #3

Foradil® Certihaler™
(formoterol fumarate inhalation powder)

Novartis Pharmaceuticals Corporation

Craig M. Bertha, Ph.D.
Division of Pulmonary and Allergy Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-592

2. REVIEW #: 3

3. REVIEW DATE: 25-OCT-2004

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	17-DEC-2002
Amendment AC	17-MAR-2003
Amendment BZ[1]	01-DEC-2003
Amendment	15-JUL-2003
Amendment	29-AUG-2003
Amendment (AZ)	24-JUN-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment BC[1]	04-OCT-2004

[1]Submission is a response to the CMC discipline review (DR) letter of 24-AUG-2004. The Division Goal date is 10-DEC-2004.

7. NAME & ADDRESS OF APPLICANT:

Name: Novartis Pharmaceuticals Corporation

Chemistry Review Data Sheet

Address:	One Health Plaza East Hanover, New Jersey 07936-1080
Representative:	Orin Tempkin, Ph.D., Global Regulatory CMC Representative
Telephone:	862-778-6949

8. DRUG PRODUCT NAME/CODE/TYPE:

a) **Proprietary Name: Foradil® Certihaler™**
b) Non-Proprietary Name (USAN): formoterol fumarate inhalation powder
c) Code Name/# (OGD only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: β_2-adrenergic bronchodilator for prevention and maintenance treatment of asthma

11. DOSAGE FORM: Inhalation Powder

12. STRENGTH/POTENCY: 5.6 mg (per actuation) of formulation contains 10 mcg (metered dose of formoterol fumarate), 8.5 mcg target emitted dose equivalent to 8.2 mcg of formoterol base; reservoir target fill of 560 mg formulation of — % w/w formoterol fumarate concentration with lactose and — % Mg stearate, — mg formoterol fumarate per reservoir b(4)

13. ROUTE OF ADMINISTRATION: oral inhalation

14. Rx/OTC DISPENSED: X Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____**SPOTS product – Form Completed**

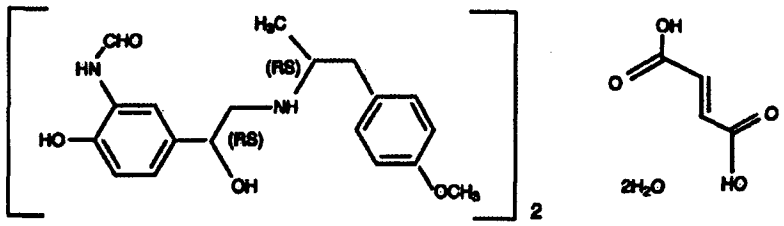
___X___Not a SPOTS product

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

(±)-2-hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]-amino]ethyl]formanilide fumarate dihydrate

$(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot 2H_2O$

Chemistry Review Data Sheet



MW = 840.9
MW = 344.414 for formoterol free-base

17. RELATED/SUPPORTING DOCUMENTS:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
				1	Adequate	7/23/04	See p. 51 in CR#1, See p. 37 in CR#2
				1	Adequate	7/21/04	See p. 96 in CR#1, See p. 102 in CR#2
				1	Adequate	10/25/04	See p. 45 in CR#1, See p. 18 in CR#2 See p. 13 in CR#3

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 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")

[2] Adequate, Inadequate, or N/A (There are enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
N20-831	Novartis Pharmaceuticals Corporation	Drug Substance	Adequate	08-Dec-2000	DS for capsule for inhalation (pre-metered) drug product using Aerolizer™ device (approved 2/16/01)

Chemistry Review Data Sheet

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	60,254	Novartis	Original IND for the current drug product

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				Consult not needed. See evaluation on p. 113 of CR#2.
EES	site inspections	21-JAN-2003	Acceptable	OC recommendation of 13-JAN-2004
Pharm/Tox				N/A
Biopharm				
LNC				N/A
Methods Validation				To be forwarded once specifications and methods finalized.
OPDRA	device trademark	16-JAN-2003	Pending	For device trademark "Certihaler™"
EA				N/A, <1 ppb expected at aquatic point of entry (p. 2, section 1-5)
Microbiology				Not needed. See evaluation on p. 86 of CR#2.

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-592

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is considered to be approvable from a CMC perspective. *Comments in the draft letter should be forwarded in a discipline review (DR) letter to the applicant by the PM as soon as feasible.*

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

The current agreements are included after the comments in the draft letter at the end of this review. Note that an additional agreement is to be confirmed via one of the comments in the draft letter.

II. Summary of Chemistry Assessments

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

The drug product is a multi-dose dry powder inhaler which is designed to deliver 60 actuations **or "shots" of the formulation. It is designed for BID usage. The product is a "device-metered"** dry powder inhaler with lactose monohydrate as the [redacted] excipient. The formulation also includes a [redacted] amount of magnesium stearate [redacted]% w/w), which is claimed to aid in [redacted]. The device has a **counter which counts down from "60" for each** individual actuation. Counting takes place after the dose is obtained and the mouthpiece cover is **put back into place. After reaching "00" the d**evice will allow the patient to receive one more actuation. After this the counter **will read "999" and the device will** lock preventing further use. If, in the future, the unit is to be approved for **"as-needed" (PRN) use, the lockout of the device** would be an issue of concern. A physician sample **variant (termed "003") is identical to the 60** count device but the lock-out occurs after 16 actuations have been used (counter set at 15 initially, see 3.2.P.8.3.2.3). b(4)

The airflow resistance of the device is [redacted] **cm $H_2O^{1/2}$/L/min (** [redacted] resistance) and is specified to actuate with a flow of [redacted] L/min (termed actuation flow rate or AFR) i.e., a metered dose will not be emitted unless the AFR is met. The mean AFR being observed for devices manufactured with [redacted] tools is 25 L/min. Usage of the device leads to about a 5 L/min increase in the AFR, which is due to [redacted] The dose content uniformity (DCU) data indicate that drug product units do not meet the [redacted]% LC mean acceptance criteria at a flow b(4) b(4)

rate of 30L/min at the beginning of unit actuations (see study on effect of flow rate on product performance on p. 18 in CR#1).

The device does not utilize any additional protective packaging (e.g., foil laminate overwrap) nor does it contain an internal desiccant. Under Agency direction the applicant undertook a stability study with protective foil overwrap in place for the DP. In summary, data did not support the use of foil laminate overwrap (for results and evaluation see p. 121 of CR#2). Also refer to the response to comment 4c in the current review regarding modification of the device counter components.

Drug product performance parameters which are key measures of quality are the DCU through-life and the aerodynamic particle size distribution (APSD).

Minor device "improvements" were made when proceeding from the clinical trial devices prepared with [redacted]; to the commercial devices prepared with [redacted] tools. For a comparison of performance data from commercial versus the clinical product see the response and evaluation to comments 7d (DCU) and 7g (APSD) in CR#2. b(4)

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

The drug product is designed to deliver 8.5 mcg of formoterol fumarate (as the dihydrate) with each actuation in a formulation of lactose with magnesium stearate. The patient is instructed to take one inhalation from the device twice a day approximately 12 hours apart (i.e., 17 mcg daily **dose). The patient's instructions for use in** the labeling recommend that the drug product **mouthpiece be cleaned with a "dry cleaning method"** on a weekly basis. The data presented in response to comment 9c of the 17-OCT-2003, AE letter supports this cleaning recommendation.

Currently the applicant is proposing a **24 month expiration dating period**, which is considered to be adequate based on the data that have been provided (see p. 113 of CR#2 for evaluation of response to comment 10d).

The current recommended storage conditions are to store at 25°C with excursions permitted from 15 to 30°C. The labeling also cautions to protect the product from heat and moisture. The product is not proposed to have any additional protective packaging (e.g., foil overwrap) nor do the data support the need for such packaging (see p. 121 of CR#2).

C. Basis for Approvability or Not-Approval Recommendation

The application is considered to be **approvable**. From a CMC perspective, approval will be recommended when the applicant adequately addresses the comments provided in the draft letter.

CMC issues to be addressed include the following:

- The acceptance criteria for the lactose monohydrate and Mg stearate excipients need revision to provide assurance of drug product reproducibility to the level seen in the drug product batches supporting the application. (draft letter comment 2 and 3)

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Craig M. Bertha, Ph.D., Review Chemist
HFD-570/820

C. CC Block

cc:
Orig. NDA 21-592
HFD-570/Division File
HFD-570/CBertha
HFD-570/RLostritto
HFD-570/AGreen
HFD-570/SBarnes

R/D Init. by: RLosttrito_____

Filename and Location: c:\data\mydocuments\reviews etc\NDA\21592\04-10-04_rev.doc

19 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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

/s/

Craig Bertha
11/4/04 08:15:36 AM
CHEMIST

See full TOC, reevaluation of 1e, example values, and revised agreement list giving dates.

Richard Lostritto
11/16/04 04:19:41 PM
CHEMIST

NDA 21-592
Chemistry Review #2

Foradil® Certihaler™
(formoterol fumarate inhalation powder)

Novartis Pharmaceuticals Corporation

Craig M. Bertha, Ph.D.
Division of Pulmonary and Allergy Drug Products

Table of Contents

APPEARS THIS WAY
ON ORIGINAL

Chemistry Review Data Sheet

1. NDA 21-592

2. REVIEW #: 2

3. REVIEW DATE: 27-JUL-2004

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	17-DEC-2002
Amendment AC	17-MAR-2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment BZ[1]	01-DEC-2003
Amendment	15-JUL-2003
Amendment	29-AUG-2003
Amendment (AZ)	24-JUN-2004

[1]Submission of a proposed clinical protocol to address functionality issues for the drug product. See minutes of 19-DEC-2003, telephone conference call with Novartis.

7. NAME & ADDRESS OF APPLICANT:

Name: Novartis Pharmaceuticals Corporation

Chemistry Review Data Sheet

Address:	One Health Plaza East Hanover, New Jersey 07936-1080
Representative:	Orin Tempkin, Ph.D., Global Regulatory CMC Representative
Telephone:	862-778-6949

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Foradil® Certihaler™
b) Non-Proprietary Name (USAN): formoterol fumarate inhalation powder
c) Code Name/# (OGD only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: β_2-adrenergic bronchodilator for prevention and maintenance treatment of asthma

11. DOSAGE FORM: Inhalation Powder

12. STRENGTH/POTENCY: 5.6 mg (per actuation) of formulation contains 10 mcg (metered dose of formoterol fumarate), 8.5 mcg target emitted dose equivalent to 8.2 mcg of formoterol base; reservoir target fill of 560 mg formulation of [redacted] % w/w formoterol fumarate concentration with lactose and [redacted] Mg stearate, [redacted] mg formoterol fumarate per reservoir b(4)

13. ROUTE OF ADMINISTRATION: oral inhalation

14. Rx/OTC DISPENSED: X Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____**SPOTS product – Form** Completed

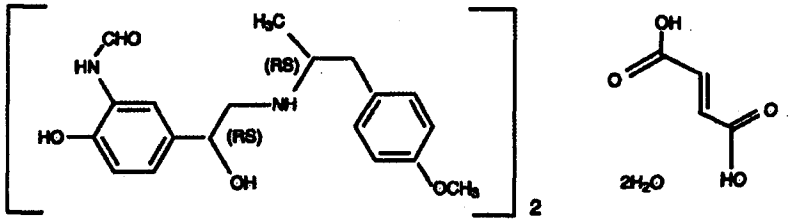
__X__Not a SPOTS product

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

(±)-2-hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]-amino]ethyl]formanilide fumarate dihydrate

$(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot 2H_2O$

Chemistry Review Data Sheet



MW = 840.9
MW = 344.414 for formoterol free-base

17. RELATED/SUPPORTING DOCUMENTS:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
[redacted]				1	Adequate	7/23/04	See p. 51 in CR#1, See p. 37 in CR#2
				1	Adequate	7/21/04	See p. 96 in CR#1, See p. 102 in CR#2
				1	Inadequate	6/30/04	See p. 45 in CR#1, See p. 18 in CR#2

b(4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 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")

[2] Adequate, Inadequate, or N/A (There are enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
N20-831	Novartis Pharmaceuticals Corporation	Drug Substance	Adequate	08-Dec-2000	DS for capsule for inhalation (pre-metered) drug product using Aerolizer™ device (approved 2/16/01)

Chemistry Review Data Sheet

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	60,254	Novartis	Original IND for the current drug product

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				Consult not needed. See evaluation on p. 113 of CR#2.
EES	site inspections	21-JAN-2003	Acceptable	OC recommendation of 13-JAN-2004
Pharm/Tox				N/A
Biopharm				
LNC				N/A
Methods Validation				To be forwarded once specifications and methods finalized.
OPDRA	device trademark	16-JAN-2003	Pending	For device trademark "Certihaler™"
EA				N/A, <1 ppb expected at aquatic point of entry (p. 2, section 1-5)
Microbiology				Not needed. See evaluation on p. 87 of CR#2.

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-592

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is considered to be approvable from a CMC perspective. *Comments in the draft letter should be forwarded in an information request (IR) letter to the applicant by the PM.*

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

See comment 6 of the attached draft letter. To be forwarded to applicant as part of information request.

II. Summary of Chemistry Assessments

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

The drug product is a multi-dose dry powder inhaler which is designed to deliver 60 actuations or "shots" of the formulation. It is designed for BID usage. The product is a "device-metered" dry powder inhaler with lactose monohydrate as the [redacted] excipient. The formulation also includes a [redacted] amount of magnesium stearate ([redacted] w/w), which is claimed to aid in [redacted]. The device has a counter which counts down from "60" for each individual actuation. Counting takes place after the dose is obtained and the mouthpiece cover is put back into place. After reaching "00" the device will allow the patient to receive one more actuation. After this the counter will read "999" and the device will lock preventing further use. If, in the future, the unit is to be approved for "as-needed" (PRN) use, the lockout of the device would be an issue of concern. A physician sample variant (termed "003") is identical to the 60 count device but the lock-out occurs after 16 actuations have been used (counter set at 15 initially, see 3.2.P.8.3.2.3). b(4)

The airflow resistance of the device is [redacted] cm $H_2O^{1/2}$/L/min ([redacted] resistance) and is specified to actuate with a flow of [redacted] L/min (termed actuation flow rate or AFR) i.e., a metered dose will not be emitted unless the AFR is met. The mean AFR being observed for devices manufactured with [redacted] tools is 25 L/min. Usage of the device leads to about a 5 L/min increase in the AFR, which is due to [redacted]. The dose content uniformity (DCU) data indicate that drug product units do not meet the [redacted]% LC mean acceptance criteria at a flow rate of 30L/min at the beginning of unit actuations (see study on effect of flow rate on product performance on p. 18 in CR#1). b(4) b(4)

The device does not utilize any additional protective packaging (e.g., foil laminate overwrap) nor does it contain an internal desiccant. Under Agency direction the applicant has a stability study with protective foil overwrap in place. In summary, data do not support the use of foil laminate overwrap (for results and evaluation see p. 121 below).

Drug product performance parameters that are key measures of quality are the DCU through-life and the aerodynamic particle size distribution (APSD).

Minor device "improvements" were made when proceeding from the clinical trial devices prepared with [redacted] to the commercial devices prepared with [redacted] tools. For a comparison of performance data from commercial versus the clinical product see the response and evaluation to comments 7d (DCU) and 7g (APSD) below. b(4)

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

The drug product is designed to deliver 8.5 mcg of formoterol fumarate (as the dihydrate) with each actuation in a formulation of lactose with magnesium stearate. The patient is instructed to take one inhalation from the device twice a day approximately 12 hours apart (i.e., 17 mcg daily dose). The patient's instructions for use in the labeling recommend that the drug product mouthpiece be cleaned with a "dry cleaning method" on a weekly basis. The data presented in response to comment 9c of the 17-OCT-2003, AE letter supports this cleaning recommendation.

Currently the applicant is proposing a 24 month expiration dating period, which is considered to be adequate based on the data that have been provided (see p. 113 for evaluation of response to comment 10d).

The current recommended storage conditions are to store at 25°C with excursions permitted from 15 to 30°C. The labeling also cautions to protect the product from heat and moisture. The product is not proposed to have any additional protective packaging (e.g., foil overwrap) nor do the data support the need for such (see p. 121).

C. Basis for Approvability or Not-Approval Recommendation

The application is considered to be **approvable**. From a CMC perspective, approval will be recommended when the applicant adequately addresses the comments provided in the draft letter.

CMC issues to be addressed include the following:

- [redacted]

b(4)

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b(4)

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•

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Craig M. Bertha, Ph.D., Review Chemist
HFD-570/820

C. CC Block

cc:
Orig. NDA 21-592
HFD-570/Division File
HFD-570/CBertha
HFD-570/RLostritto
HFD-570/AGreen
HFD-570/SBarnes

R/D Init. by: RLosttrito_____

Filename and Location: c:\data\mydocuments\reviews etc\NDA\21592\04-06-24_rev.doc

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X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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

/s/

Craig Bertha
8/9/04 03:10:15 PM
CHEMIST

Richard Lostritto
8/11/04 12:25:44 PM
CHEMIST

NDA 21-592

Foradil® Certihaler™
(formoterol fumarate inhalation powder)

Novartis Pharmaceuticals Corporation

Craig M. Bertha, Ph.D.
Division of Pulmonary and Allergy Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-592

2. REVIEW #: 1

3. REVIEW DATE: 01-Apr-2003

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	17-Dec-2002
Amendment AC[1]	17-Mar-2003

b(4)

7. NAME & ADDRESS OF APPLICANT:

Name:	Novartis Pharmaceuticals Corporation
Address:	One Health Plaza East Hanover, New Jersey 07936-1080
Representative:	Ann Shea, Associate Director, Drug Regulatory Affairs
Telephone:	862-778-4567

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Foradil® Certihaler™
b) Non-Proprietary Name (USAN): formoterol fumarate inhalation powder
c) Code Name/# (OGD only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: β_2-adrenergic bronchodilator for prevention and maintenance treatment of asthma

11. DOSAGE FORM: Inhalation Powder

12. STRENGTH/POTENCY: 5.6 mg (per actuation) of formulation contains 10 mcg (metered dose of formoterol fumarate), 8.5 mcg target emitted dose equivalent to 8.2 mcg of formoterol base; reservoir target fill of 560 mg formulation of [redacted] % w/w formoterol fumarate concentration with lactose and [redacted] % Mg stearate, [redacted] mg formoterol fumarate per reservoir

13. ROUTE OF ADMINISTRATION: oral inhalation

14. Rx/OTC DISPENSED: X Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

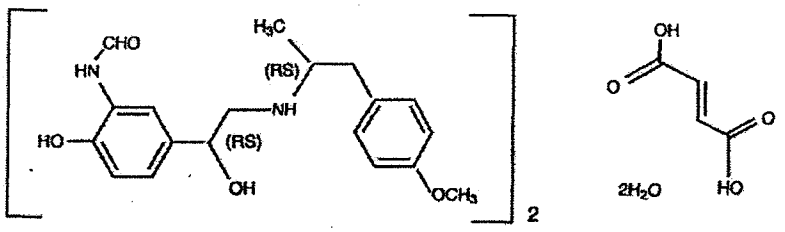
_____SPOTS product – Form Completed

__X__Not a SPOTS product

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

(±)-2-hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]-amino]ethyl]formanilide fumarate dihydrate

$(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot 2H_2O$



MW = 840.9
MW = 344.414 for formoterol free-base

17. RELATED/SUPPORTING DOCUMENTS:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
[redacted]				1	Inadequate	2/11/03	Def. letter sent, see p. 51 in CR#1
				1	Inadequate	3/19/03	Def. letter sent, see p. 96 in CR#1
				1	Inadequate	2/3/03	Def. letter sent, see p. 45 in CR#1

b(4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
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5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

Chemistry Review Data Sheet

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
N20-831	Novartis Pharmaceuticals Corporation	Drug Substance	Adequate	08-Dec-2000	DS for capsule for inhalation (pre-metered) drug product using Aerolizer™ device (approved 2/16/01)

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	60,254	Novartis	Original IND for the current drug product

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				Will be forwarded when DP specifications finalized.
EES	site inspections	21-Jan-2003	Pending	
Pharm/Tox				N/A
Biopharm				
LNC				N/A
Methods Validation				To be forwarded once specifications and methods finalized.
OPDRA	device trademark	16-Jan-2003	Pending	For device trademark "Certihaler™"
EA				N/A, <1 ppb expected at aquatic point of entry (p. 2, section 1-5)
Microbiology				Not needed prior to finalization of microbial limits specifications.

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-592

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is considered to be approvable from a CMC perspective. Comments in the draft letter should be forwarded to the applicant and should be adequately addressed prior to the approval of the application.

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

None recommended at this time.

II. Summary of Chemistry Assessments

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

The drug product is a multi-dose dry powder inhaler which is designed to deliver 60 actuations or "shots" of the formulation. The device has a counter which counts down from "60" for each individual actuation. Counting takes place after the dose is obtained and the mouthpiece cover is put back into place. After reaching "00" the device will allow the patient to receive one more actuation. After this the counter will read "999" and the device will lock preventing further use. If, in the future, the unit is to be approved for as-needed (PRN) use, the lockout of the device could be an issue of concern. A physician sample variant (termed "003") is identical to this but has a lock-out after 16 actuations have been used (counter set at 15 initially, see 3.2.P.8.3.2.3).

The airflow resistance of the device is [redacted] cm $H_2O^{1/2}$/L/min ([redacted] resistance) and the patient must generate a flow of [redacted]/min (termed actuation flow rate or AFR) before the device is activated (i.e., a metered dose is allowed to be emitted). The dose content uniformity (DCU) data indicate that drug product units do not meet the [redacted] % LC mean acceptance criteria at a flow rate of 30L/min at the beginning of unit actuations (see study on effect of flow rate on product performance on p. 18 below). b(4)

The device does not utilize any additional protective packaging (e.g., foil laminate overwrap) nor does it contain an internal desiccant. Under Agency direction the applicant has started a stability study with protective foil overwrap in place (see p. 128 below).

Key drug product performance parameters that impact on quality are the DCU and the aerodynamic particle size distribution (APSD).

Minor device "improvements" were made when proceeding from the clinical trial devices prepared with [redacted] to the commercial devices prepared with [redacted] tools. Very limited data available on devices prepared with the [redacted] tools.

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

The drug product is designed to deliver 8.5 mcg of formoterol fumarate (as the dihydrate) with each actuation in a formulation of lactose with magnesium stearate. The patient is instructed to take one inhalation from the device twice a day approximately 12 hours apart (i.e., 17 mcg daily dose). Currently the applicant is proposing a 24 month expiration dating period, however, until the drug product specifications are finalized, a consult of the stability data to our biometrics team will not be forwarded. The current recommended storage conditions are to store at 25°C with excursions permitted from 15 to 30°C. The labeling also cautions to protect from heat and moisture.

C. Basis for Approvability or Not-Approval Recommendation

The application is considered to be **approvable**. From a CMC perspective, approval will be recommended when the applicant adequately addresses the comments provided in the draft letter.

CMC issues include the following:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

b(4)

b(4)

- There are preliminary comments regarding the labels and labeling that will be forwarded regarding CMC related concerns.

- The EES recommendation for the application is currently pending from OC.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Craig M. Bertha, Ph.D., Review Chemist
HFD-570/820

C. CC Block

cc:
Orig. NDA 21-592
HFD-570/Division File
HFD-570/CBertha
HFD-570/GPoochikian
HFD-570/COstroff
HFD-570/SBarnes

R/D Init. by: GPoochikian_____

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_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Craig Bertha
4/28/03 09:16:20 AM
CHEMIST

Guiragos Poochikian
4/28/03 09:20:33 AM
CHEMIST