

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-527

CHEMISTRY REVIEW(S)



NDA 21-527
Chem. Rev. # 2

Atrovent HFA

Boehringer Ingelheim Pharmaceuticals, Inc.

Prasad Peri, Ph.D.
Division of New Drug Chemistry II
Office of New Drug Chemistry

Division of Pulmonary and Allergy Drug Products



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Chemistry Review Data Sheet

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1. NDA 21-527
2. REVIEW #: 2
3. REVIEW DATE: 16 Nov. 2004
4. REVIEWER: Prasad Peri
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

Original	6-Dec-02
Amendment (Responses to fax dated 26-Feb-03)	24-Mar-03
Amendment (Responses to fax dated 4-Mar-03)	12-Mar-03
Amendment (Responses to fax dated 4-Mar-03)	21-Mar-03

6. SUBMISSION(S) BEING REVIEWED:

Amendment (Responses to May 6, 2003)	1-Oct-2003
Amendment (Stability Update)	2-Oct-2003
Amendment (Responses to AE Letter dated Oct. 9, 2003)	14-May-2004
Amendment (LOAs for confidential disclosure of DMF information to the applicant)	25-Jun-2004
Amendment (Responses to AE Letter dated Oct. 9, 2003, & comment 37n)	3-Sep-2004
Amendment (Responses to Telecon dated May 7, 2004)	3-Sep-2004
Amendment (Responses to Faxes dated Oct. 22, 2004 and Oct. 28, 2004)	26-Oct-2004
Amendment (Responses to Faxes dated Oct. 22, 2004 and Oct. 28, 2004)	29-Oct-2004
Amendment (Responses to CMC Information from teleconference dated and Oct. 29, 2004)	1-Nov-2004

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Amendment (Responses to Fax dated Nov. 8, 2004)	10-Nov-2004
Amendment (Responses to Labeling comments dated Nov. 10, 2004)	12-Nov-2004

7. NAME & ADDRESS OF APPLICANT:

Name: Boehringer Ingelheim Pharmaceuticals, Inc.
Address: 900 Ridgebury Road, PO Box 368
Ridgefield, CT 06877-0368
Representative: Jeffrey R Snyder
Telephone: (203) 798 9988

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Atrovent HFA Inhalation Aerosol
- b) Non-Proprietary Name (USAN): Ipratropium bromide HFA Inhalation Aerosol
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - ? Chem. Type: 3
 - ? Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Section 505(b)(1) of the FD&C Act

10. PHARMACOL. CATEGORY: Anticholinergic (parasympatholytic)
Bronchodilator

11. DOSAGE FORM: Aerosol, metered (code 339)

12. STRENGTH/POTENCY: Net weight 12.9 gm/canister, 21 µg of active from
valve and — µg of active from mouthpiece per
actuation, 200 actuations per can

13. ROUTE OF ADMINISTRATION: Oral Inhalation

14. Rx/OTC DISPENSED: X Rx ___ OTC

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

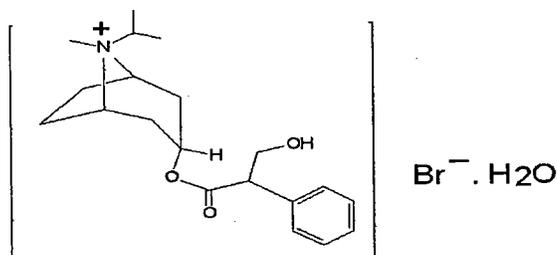
CHEMISTRY REVIEW

Chemistry Review Data Sheet

____ SPOTS product – Form Completed

X Not a SPOTS product

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



Systematic Name: 1-alpha-H,5-alpha-H-Tropanium, 3-alpha-hydroxy-8-isopropyl-, bromide, (±)-tropate

Molecular Formula: $\text{C}_{20}\text{H}_{30}\text{NO}_3\text{Br} \cdot \text{H}_2\text{O}$

Molecular Weight: 430.4

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS ³
U	II		/	3	Adequate	7/7/2003	
	III			3	Adequate	2/21/2002	No significant change in the DMF since the last review
	V			1	Adequate	Information has been forwarded to Pharm/Tox	Adequate per the Pharmacologist Dr. Whitehurst.
	III			1	Inadequate Adequate	9/29/2003 11/15/2004	Def. Letter sent. IR letter sent
	III			1	Inadequate Adequate	10/7/2003 11/9/2004	Def. Letter sent.
	III			1	Inadequate Adequate	8/26/2003 11/9/2004	Def. Letter sent. IR Letter sent
	III			1	Inadequate Adequate	10/2/2003 11/9/2004	Def. Letter sent. IR letter sent
	III			1	Adequate	8/27/2003	

CHEMISTRY REVIEW

Chemistry Review Data Sheet

/	III	/	/	3	Adequate	12/29/2000	
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¹ Action codes for DMF Table: * Review will be completed prior to final action date.

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 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

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS
NDA 19-085	BIPI	Atrovent Inhalation Aerosol CFC	approved
NDA 20-393	BIPI	Atrovent Nasal Spray 0.03%	approved
NDA 20-394	BIPI	Atrovent Nasal Spray 0.06%	approved
NDA 20-228	BIPI	Atrovent Inhalation Solution	approved
NDA 20-291	BIPI	Combivent Inhalation Aerosol CFC	approved

18. CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	Shelf Life Stability	Determined not necessary.		N/A
EES	DS and DP Sites *	12/24/02	Adequate for all sites per July 2, 2003 OC recommendation	Adequate for all sites
Pharm/Tox	Citric Acid, Safety Data for HFA 134a	1/9/2003 (email)	Dr. Virgil Whitehurst, completed 1/15/2003	No concerns per Dr. Whitehurst's evaluation.
	Citric Acid	10/7/03	Dr. Tim McGovern, completed 10/7/2003	No safety concerns per Dr. McGovern's evaluation of 10/7/03
	Leachables in the drug product	9/28/2004	Completed, 11/2/2004 Leachables acceptance criteria for the drug product are acceptable except for	Applicant has reduced the acc. criterion for to canister till adequate qualification studies are conducted.
	Particulate matter in the DP	8/01/03	Dr. Virgil Whitehurst Completed 10/6/2003	Deficient. Issues related to need to be resolved.
Biopharm	N/A			
LNC	N/A			
Methods Validation	Pending approval of application			Will be sent after approval of application
OPDRA	Safety evaluation	Sent by PM		Acceptable

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Chemistry Review Data Sheet

EA	Exclusion requested	See Chem. Rev. 1	Acceptable
Microbiology	N/A		Not necessary per data.

Site	CFN #	Responsibilities	Status
BI Pharma KG, Germany	9610492	DS Mfg Site and DS Testing Site	Acceptable on 12/31/2002
			Acceptable 01/15/2003
3M Pharmaceuticals, Northridge, CA	2010441	Testing of excipients, Manufacture of bulk drug product (aerosol canister), Testing of drug product (release and stability)-except tests for leachables and	Acceptable 6/20/2003
3M Pharmaceuticals, St. Paul, MN	2126770	Testing of excipients (HFA134a) , Testing of drug product (release and stability)-except tests for leachables and	Acceptable 7/02/2003
			Acceptable on 12/26/2002
			Acceptable on 12/26/2002
			Acceptable on 12/31/2002
			Acceptable on 9/29/2004

CHEMISTRY REVIEW

Chemistry Assessment Section

The Chemistry Review for NDA 21-527

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approval from a CMC standpoint

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

Several Phase 4 agreements have been provided for and are listed at the end of the review (page 171). Some of them are highlighted in the Drug product section.

II. Summary of Chemistry Assessments

Note that the CMC section of the NDA consisted of 20 volumes and approximately 68 reports. An overall, unified discussion of the information in these separate reports was not provided. Very preliminary issues related to lack of adequate *in vitro* comparability of the three generations of products were identified at the NDA filing meeting and communicated to the applicant in the 75 day letter.

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

Drug Substance

All information pertaining to manufacture, packaging, testing etc. of the drug substance is referenced to DMF — This DMF has been reviewed and was found adequate on 2/25/03.

Ipratropium bromide monohydrate is a white to off-white crystalline powder. The drug substance has one chiral center and is provided as a

Ipratropium bromide has previously been approved in the following NDAs:

<u>NDA</u>	<u>Drug Name</u>	<u>Applicant</u>
19-085	Atrovent MDI	Boehringer Ingelheim
20-228	Atrovent Liquid for Inhalation	Boehringer Ingelheim
20-291	Combivent MDI	Boehringer Ingelheim
20-393	Atrovent Nasal Spray	Boehringer Ingelheim
20-394	Atrovent Nasal Spray	Boehringer Ingelheim
20-950	DuoNeb Liquid for Inhalation	Dey

Since the application under review utilizes ipratropium as a solution in ethanol, and HFA 134a, with small amounts of water and citric acid added there are no issues with polymorphism, particle size distribution and other physical properties that are critical to a suspension formulation. Since the formulation is a solution, the drug substance is not micronized. There are no significant drug substance-related issues at this time.

CHEMISTRY REVIEW

Chemistry Assessment Section

Drug Product

The drug product is a **solution metered-dose inhaler (MDI)** manufactured for BIPI by 3M Pharmaceuticals at their Northridge, CA facility. 3M Pharmaceuticals (Northridge facility) also manufactures Atrovent CFC MDI, and Combivent CFC MDI which are other BIPI products. The proposed commercial name for the drug product is Atrovent HFA (Ipratropium Bromide HFA) Inhalation Aerosol 12.9 gm, — µg/actuation (17 µg/actuation for labeling purpose) through the mouthpiece and 21 µg/actuation through the valve. The drug product will be manufactured in only one strength and labeled to provide 200 actuations per canister. Each canister will be overfilled to a target fill weight of — gm which will provide up to — theoretical actuations. The applicant proposed a shelf life for the drug product to be —. However, due to existing levels of the leachable — in the drug product, a shelf life of 18 months has been approved.

The solution formulation contains unmicronized Ipratropium bromide monohydrate, anhydrous citric acid, dehydrated ethanol, purified water, and HFA-134a (1,1,1,2-tetrafluoroethane) as the propellant. Ethanol functions as a — and citric acid — for this ester drug substance. BIPI claims that the small amount of water present is used

The components of the valve are fabricated from — () stainless steel (canister), and

The actuator components are the mouthpiece (white), sleeve (colorless), and a dust cap (green), each made of —. The spray orifice diameter (SOD) for the actuator is — in. The development of this drug product has seen several changes in the container closure system (first, second, and third generation products). These changes and their consequences have been highlighted in Chemistry Review 1. These changes resulted in the generation of a greater portion of the dose as the fine particle fraction for the to be marketed delivery device. In addition, improvement in the valve rubber formulation also resulted in reduced extractable/leachables seen in the drug product.

Due to insufficient information on the safety, quality, and methods for the analysis of the drug product, the application could not be approved during the first cycle. Several DMFs were found inadequate in the first cycle as well. All safety and quality issues have been resolved in this cycle.

During the second review cycle, several agreements for post approval studies were made with the applicant. They are listed on page 171 of this review. Some of main agreements are briefly listed below.

- ✘ BIPI agrees to conduct an additional 90-day toxicology study in rats that will seek to specifically qualify leachables in the drug product. The current acceptance criterion for the leachable — (NMT — /canister) is based on previous data that is within the Division's knowledge from other applications. The data provided for this leachable was not adequate to make a safety assessment above the proposed limit for —.
- ✘ BIPI will conduct stability study to confirm and fully characterize the inherent variability in the aerodynamic particle size distribution (APSD) when the drug product is placed at 40°C/85% RH conditions for up to —. Results provided to date pointed to some

CHEMISTRY REVIEW

Chemistry Assessment Section

significant change in the APSD profile under the above mentioned storage conditions and the applicant claims that these are related to inherent variability.

- ✍ BIPI agrees to conduct a post approval stability study and provide and evaluate data for foreign particulates as a function of time, on the three validation/commercial batches of drug product. Previous data provided were from studies at a single time point with not trend analysis. Hence no acceptance criteria were proposed for the particulate matter.
- ✍ BIPI agrees to adopt interim specifications for APSD _____, for a period of 12 months from the date of approval of our NDA.
- ✍ Within 12 months of approval of the application, a leachable specification for _____ will be added to the drug product specification.
- ✍ Within 12 months of approval of the application, BI will propose tightened acceptance criteria for the spray pattern test in the drug product specification.
- ✍ BI agrees that the shelf life will not be extended via the NDA Annual Report. Any shelf life extension will be the subject of a Prior Approval Supplement.
- ✍ See detailed list of agreements on page 171 herein.

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

The drug product is a "press and breathe MDI" for oral inhalation. Therefore, it requires some patient coordination. This drug product does not use of a spacer between the mouthpiece of the device and the patient's mouth. The drug product is produced in one strength of ipratropium bromide and is labeled for 200 doses of ipratropium bromide monohydrate at _____ μg /actuation through the mouthpiece. The proposed maximum daily recommended dose is 201.6 micrograms (6 doses or 12 inhalations) of ipratropium bromide monohydrate. Patients are to prime the canister twice prior to taking the first dose and when the inhaler has not been used for 3 days (72 hours). Patients are advised to clean the mouthpiece at least once a week with water and dried thoroughly prior to use. Cleaning, priming and re-priming instructions are adequately supported by data. Patients are advised to store the drug product at 25°C (77°F). Excursions between 15°C (59°F) and 30°C (86°F) are permitted.

C. Basis for Approvability or Not-Approval Recommendation

The application is recommended for an Approval action in the current form. Several phase 4 agreements are in place and are highlighted at the end of the review (page 171).

III. Administrative

A. Reviewer's Signature

Prasad Peri, Ph.D.

B. Endorsement Block

C. CC Block

171 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

MEMORANDUM: DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC
HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 28-MAY-2004

TO: Prasad Peri, Ph.D.
Alan Schroeder, Ph.D.
Brian Rogers, Ph.D.
Chemistry Reviewers
Division of Pulmonary Drug Products (HFD-570)



THROUGH: Richard T. Lostritto, Ph.D.
Chemistry Team Leader
Division of Pulmonary Drug Products (HFD-570)

FROM: Craig M. Bertha, Ph.D.
Chemistry Reviewer
Division of Pulmonary Drug Products (HFD-570)

SUBJECT: Preliminary Review of 14-MAY-2004, Amendment in response to 09-OCT-2003,
AE letter

APPLICATION:

Atrovent HFA (ipratropium bromide) Inhalation Aerosol (N21-527) from Boehringer Ingelheim
(BI)

LAST ACTION: Approvable letter of 09-OCT-2003

COMPLETENESS OF RESPONSE:

All of the comments included in the 09-OCT-2003, AE letter, with the exception of the last comment 42, which referred to draft labeling comments from all disciplines, were CMC-related. Preliminary review of the four-volume response to the AE letter does support the applicant's contention that the response is complete. However, the status of the supporting DMFs is problematic (see below).

STATUS AND REQUEST FOR DMFs:

As of the date of the last chemistry review of 20-OCT-2003, there were four of nine supporting DMFs with inadequate status:

<u>DMF #</u>	<u>Type</u>	<u>Holder</u>	<u>Item Referenced</u>	<u>Reviewer/Date</u>
--------------	-------------	---------------	------------------------	----------------------

III
 III
 III
 III

A. Schroeder/29-SEP-2003
 P. Peri/07-OCT-2003
 P. Peri/26-AUG-2003
 P. Peri/02-OCT-2003

Our files show that there were deficiency letters dated 29-AUG-2003, and 23-OCT-2003, for DMFs — and — respectively. These holders have been contacted since no responses have been submitted and they claim not to have received the letters. The PM has been asked to resend both of these letters.

Also, it was determined that deficiency letters resulting from the reviews of DMFs — and — were never forwarded to the holders of these files. The PM has been requested to expedite these letters such that the holders will have sufficient time to respond.

The applicant was not informed in the AE letter that these DMFs were deficient and as such, has not directly addressed the status of any supporting DMFs in the response. Note that the response to the AE letter comment 29 did make reference to information contained in DMF — however.

INITIAL ASSESSMENT OF RESPONSES REGARDING CRITICAL CMC ISSUES:

Based on this preliminary review of the applicant's response, there are, in my opinion, four critical issues for this application that should be addressed first during the review and which may need to be the subject of IR letter comments. These four issues are listed below in order of their priority:

- New leachables methods (comments 12i, j, 14b) and evaluation of extractables/leachables correlation [comment 11j(2) and 33f] and acceptance criteria (responses to comments 29, 30, 31, 32a, b, 33a-e, g, h, 34, 37a-c, i-n, 40, 41 are also related to leachables and should be examined as part of the overall assessment);
- Aerodynamic particle size distribution (APSD) testing and acceptance criteria (comment 11h); APSD mass balance [comment 12h(5)];
- Proposal to eliminate spray pattern testing (comments 11k and 38b-d);
- New DP degradant method [comment 12e(1)-(3), 14b].

An initial assessment of the applicant responses to these comments is captured below.

Agency Comments 12i and 12j

Comment 12i

The following comments pertain to the method for quantitation of extractables and leachables — in the drug product.

10 Page(s) Withheld

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

_ § 552(b)(5) Deliberative Process

_ § 552(b)(4) Draft Labeling

CONSULTS REQUESTED:

No new sites are discussed in the current amendment that would require an update to the EES for the application. The overall compliance recommendation was ACCEPTABLE and this is dated 02-JUL-2003. Based on the multitude of clarifications, deficiencies, and information requested regarding the extractables/leachables characterization and controls, it is not possible at this time to formulate a consult to the P/T team prior to a detailed review of the submitted data and information. In the opinion of this reviewer, this is the most critical issue identified since it will likely require the most review and negotiation for resolution prior to approval.

CONCLUSION/RECOMMENDATIONS:

- The amendment is considered to be a complete response relative to the CMC comments included in the 09-OCT-2003, AE letter. However, the AE letter should have informed the applicant that there were four DMFs supporting the application that were reviewed and found to be inadequate.
- With regard to the four deficient DMFs, none of the holders claim to have received the Agency deficiency letters. It is clear that the deficiency letters for DMFs did not issue. The PM has been requested to expedite the issuance of all of these letters.
- The response has been examined and the key issues involve: 1) the characterization and control of extractables/leachables; 2) APSD testing and acceptance criteria; 3) applicants proposal to eliminate spray pattern testing for the DP and incoming actuator component; 4) a new method for determination of DP impurities.
- No request for inspection via EES is deemed necessary at this time.
- It is recommended that the reviewer first focus on the extractables/leachables issues such that a consult for safety of the permitted maximum daily intake of these undesirable components (based on extractables/leachables acceptance criteria) can be forwarded to the P/T team as soon as it is feasible.
- Based on a preliminary examination of the data provided in the 02-OCT-2003, amendment containing the stability update, it is suspected that even with some warranted tightening of the acceptance criteria of the APSD, the expiry proposed by the applicant will be supportable. It is recommended that once the APSD specifications are finalized, the reviewer submit the data to the biometrics team for their analysis. With regard to the applicant's proposal for a expiry, it is not seen to be the best use of Agency resources to include in the biometrics consult a request for analysis for any of the other parameters, based on this reviewers preliminary examination of that data package. However, it may be worthwhile asking the biometrics team to spot-check the statistical analysis that has already been provided by the applicant to verify that it was performed in an acceptable manner.

Craig M. Bertha, Ph.D.
Chemistry Reviewer

cc:

Orig. NDA 21-527

HFD-570/Div. Files

HFD-570/CBertha 5/28/04

HFD-570/PPeri

HFD-570/ASchroeder

HFD-570/BRogers

HFD-570/RLostritto

HFD-570/LJafari

**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
6/7/04 05:46:38 AM
CHEMIST

Richard Lostritto
6/9/04 06:12:49 PM
CHEMIST



NDA 21-527

Atrovent HFA

Boehringer Ingelheim Pharmaceuticals, Inc.

Prasad Peri, Ph.D.

Brian Rogers, Ph.D.

Alan Schroeder, Ph.D.

Division of New Drug Chemistry II

Office of New Drug Chemistry

Division of Pulmonary and Allergy Drug Products



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1. NDA 21-527

2. REVIEW #: 1

3. REVIEW DATE: 8-Oct, 2003

4. REVIEWERS: Brian D Rogers (Drug Substance)
Alan C Schroeder (Drug Product-Container Closure System)
Prasad Peri (Drug Product)

5. PREVIOUS DOCUMENTS:

Previous Documents

None

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Original	6-Dec-02
Amendment (Responses to fax dated 26-Feb-03)	24-Mar-03
Amendment (Responses to fax dated 4-Mar-03)	12-Mar-03
Amendment (Responses to fax dated 4-Mar-03)	21-Mar-03

7. NAME & ADDRESS OF APPLICANT:

Name: Boehringer Ingelheim Pharmaceuticals, Inc.

Address: 900 Ridgebury Road, PO Box 368
Ridgefield, CT 06877-0368

Representative: Jeffrey R Snyder

Telephone: (203) 798 9988

CHEMISTRY REVIEW

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Atrovent HFA Inhalation Aerosol
- b) Non-Proprietary Name (USAN): Ipratropium bromide monohydrate HFA Inhalation Aerosol
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Section 505(b)(1) of the FD&C Act

10. PHARMACOL. CATEGORY: Anticholinergic (parasympatholytic)
Bronchodilator

11. DOSAGE FORM: Aerosol, metered (code 339)

12. STRENGTH/POTENCY: Net weight 12.9 gm/canister, 21 μg of active from valve and — μg of active from mouthpiece per actuation, 200 actuations per can

13. ROUTE OF ADMINISTRATION: Oral Inhalation

14. Rx/OTC DISPENSED: Rx OTC

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

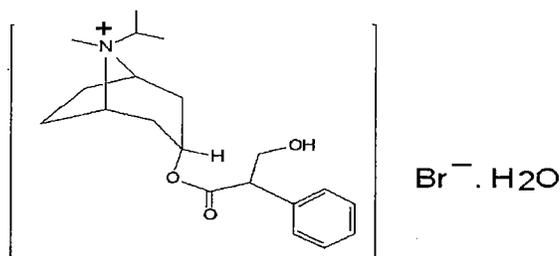
SPOTS product – Form Completed

Not a SPOTS product

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

CHEMISTRY REVIEW

Chemistry Review Data Sheet



Systematic Name: 1-alpha-H,5-alpha-H-Tropanium, 3-alpha-hydroxy-8-isopropyl-, bromide, (±)-tropate

Molecular Formula: $\text{C}_{20}\text{H}_{30}\text{NO}_3\text{Br} \cdot \text{H}_2\text{O}$

Molecular Weight: 430.4

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS ³
	II			3	Adequate	7/7/2003	
	III			3	Adequate	2/21/2002	No significant change in the DMF since the last review
	V			1	Adequate	Information has been forwarded to PharTox	Adequate per the Pharmacologist Dr. Whitehurst.
	III			1	Inadequate	9/29/2003	Def. Letter sent.
	III			1	Inadequate	10/7/2003	Def. Letter to be sent.
	III			1	Inadequate	8/26/2003	Def. Letter sent.
	III			1	Inadequate	10/2/2003	Deficiency Letter sent.
	III			1	Adequate	8/27/2003	
	III			3	Adequate	12/29/2000	

¹ Action codes for DMF Table: * Review will be completed prior to final action date.

1 – DMF Reviewed.

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

2 – Type 1 DMF

CHEMISTRY REVIEW

Chemistry Review Data Sheet

- 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 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

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
NDA 19-085	BIPI	Atrovent Inhalation Aerosol CFC	approved		
NDA 20-393	BIPI	Atrovent Nasal Spray 0.03%	approved		
NDA 20-394	BIPI	Atrovent Nasal Spray 0.06%	approved		
NDA 20-228	BIPI	Atrovent Inhalation Solution	approved		
NDA 20-291	BIPI	Combivent Inhalation Aerosol CFC	approved		

18. CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	Shelf Life Stability	Withheld pending applicants response to deficiencies in the review.		N/A
EES	DS and DP Sites *	12/24/02	Adequate for all sites per July 2, 2003 OC recommendation	Adequate for all sites
Pharm/Tox	Citric Acid, Safety Data for HFA 134a	1/9/2003 (email)	Dr. Virgil Whitehurst, completed 1/15/2003	No concerns per Dr. Whitehurst's evaluation.
	Citric Acid	10/7/03	Dr. Tim McGovern , completed 10/7/2003	No safety concerns per Dr. McGovern's evaluation of 10/7/03
	Leachables in the drug product	Pending applicants responses	Pending submission	Consult for extractables/leachables is deferred pending applicants responses to our deficiencies
	Particulate matter in the DP	8/01/03	Dr. Virgil Whitehurst Completed 10/6/2003	Deficient. Issues related to need to be resolved.
Biopharm	N/A			
LNC	N/A			
Methods Validation	To be sent pending adequate responses to deficiencies			Will be sent after specifications issues are resolved
OPDRA	N/A			Not necessary per data.
EA	Exclusion requested	See Chem. Rev. 1		Acceptable
Microbiology	N/A			Not necessary per data.

CHEMISTRY REVIEW

Chemistry Review Data Sheet

Site	CFN #	Responsibilities	Status
BI Pharma KG, Germany	9610492	DS Mfg Site and DS Testing Site	Acceptable on 12/31/2002
3M Pharmaceuticals, Northridge, CA	2010441	Testing of excipients, Manufacture of bulk drug product (aerosol canister), Testing of drug product (release and stability)-except tests for leachables and	Acceptable 01/15/2003
3M Pharmaceuticals, St. Paul, MN	2126770	Testing of excipients (HFA134a) , Testing of drug product (release and stability)-except tests for leachables and	Acceptable 7/02/2003
			Acceptable on 12/26/2002
			Acceptable on 12/26/2002
			Acceptable on 12/31/2002

CHEMISTRY REVIEW

Executive Summary Section

The Chemistry Review for NDA 21-527

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approval from a CMC standpoint

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

None indicated so far

II. Summary of Chemistry Assessments

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

Note that the CMC section of the NDA consisted of 20 volumes and approximately 68 reports. An overall, unified discussion of the information in these separate reports was not provided. Very preliminary issues related to lack of adequate *in vitro* comparability of the three generations of products were identified at the NDA filing meeting and communicated to the applicant in the 75 day letter.

Drug Substance

All information pertaining to manufacture, packaging, testing etc. of the drug substance is referenced to DMF — This DMF has been reviewed and was found adequate on 2/25/03.

Ipratropium bromide monohydrate is a white to off-white crystalline powder —
— The drug substance has one chiral center and is provided as a

Ipratropium bromide has previously been approved in the following NDAs:

NDA	Drug Name	Applicant
19-085	Atrovent MDI	Boehringer Ingelheim
20-228	Atrovent Liquid for Inhalation	Boehringer Ingelheim
20-291	Combivent MDI	Boehringer Ingelheim
20-393	Atrovent Nasal Spray	Boehringer Ingelheim
20-394	Atrovent Nasal Spray	Boehringer Ingelheim
20-950	Duoneb Liquid for Inhalation	Dey

Since the application under review utilizes ipratropium as a solution in water, ethanol, citric acid, and HFA 134a, there are no issues with polymorphism, particle size distribution and other physical properties that are critical to a suspension formulation. Since the formulation is claimed to be a solution, the drug substance is not micronized. There are no significant drug substance-related issues at this time.

CHEMISTRY REVIEW

Executive Summary Section

Drug Product

The drug product is a solution metered-dose inhaler (MDI) being manufactured for BIPI by 3M Pharmaceuticals at their Northridge, CA facility. 3M Pharmaceuticals (Northridge facility) also manufactures Atrovent CFC MDI, and Combivent CFC MDI which are other BIPI products. The proposed commercial name for the drug product is Atrovent HFA (Ipratropium Bromide HFA) Inhalation Aerosol 14 gm, — $\mu\text{g}/\text{actuation}$ through the mouthpiece and 21 $\mu\text{g}/\text{actuation}$ through the valve. However the Agency recommends that the label be changed to state 17 $\mu\text{g}/\text{actuation}$ based on the release data from the primary stability batches. The drug product will be manufactured in only one strength and labeled to provide 200 actuations per canister. Each canister will be overfilled to a target fill weight of — which will provide — theoretical actuations. The proposed shelf life of the drug product is — and the Agency has not reached an agreement on this proposal pending evaluation of pending data. The drug product is not packaged in a secondary over wrap foil.

The formulation contains unmiconized Ipratropium bromide monohydrate, anhydrous citric acid, dehydrated ethanol, purified water, and HFA-134a. HFA-134a (1,1,1,2-tetrafluoroethane) is the only propellant and contributes to the vapor pressure inside the canister. Ethanol functions as a — and citric acid — for the formulation. BIPI claims that the small amount of water present —

The components of the valve are fabricated from —

The components of the actuator are the mouthpiece (white), sleeve (colorless), and a dust cap (green) each made of polypropylene. The spray orifice diameter (SOD) for the actuator is —

The development of this drug product has seen several changes in the container closure system (first, second, and third generation products).

Significant changes in the three generation products include

Manufacturing Process/Site

1. —
2. Change in manufacturing site from BI Production (Germany and USA) to 3 M production (Northridge, CA).

Container Closure System

1. Change in the — valve stem to a — valve stem from 1st to 2nd generation
2. Change in the internal diameter from —
3. Change in the composition of the Stainless steel alloy for canister (—)
4. Change in the composition of the —
5. Change in the manufacturer of the Valve —
6. Change in supplier and formulation of — valve seals / —

CHEMISTRY REVIEW

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7. The composition of the stainless steel canister was modified from the first generation product

Formulation changes during the drug development program were very minor.

Most Significant Consequences of the change

Note that most of the safety and efficacy studies were performed with the 1st generation product. Changes in the valve have affected the performance of the drug product particularly in the aerodynamic particle size distribution.

Due to the change in the internal diameter of the valve stem from the first generation to the second generation, the mass of the ipratropium bromide collected on the filter (particles typically _____ on the Andersen Cascade Impactor) increased by _____. This increase was reflected by a decrease in mass of ipratropium collected on _____ (typically particles in the range of _____).

The complete impact of the changes in the container closure system on the Aerodynamic Particle Size Distribution (APSD) of the drug product was difficult to evaluate due to the following issues.

1. Current lack of availability of the drug product from the first and second generation products (e.g., for additional comprehensive testing). The first generation product was manufactured in 1994 and second generation product was manufactured in 1996.
2. Change in *in-vitro* methods for measuring the APSD between the first, second and third generation products. A comparison of the first and third generation products used _____ and a comparison between the second and third generation products used _____.

BIPI has provided an indirect link comparing the first and third generation products by performing *in-vitro* testing on _____ with the third generation products. The results of this testing indicate that more than _____ mass of ipratropium is collected on the filter using the _____ as compared to the _____.

The conclusion for this issue is that due to the absence of a direct *in-vitro* comparison between the three generations of products, some APSD differences in the drug product over its development may be masked. This information was discussed with all the other disciplines during several in-house meetings. The Medical officers are aware of the differences and they will decide if they have sufficient clinical and pharmacokinetic data to bridge them. CMC comments regarding lack of in vitro comparison between the three generation of products have been documented in the CMC memo signed off in DFS.

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

The drug product is to be inhaled orally and requires some patient coordination. The applicant does not describe the use of a spacer between the mouthpiece of the device and the patient's mouth. The drug product is produced in one strength of ipratropium bromide and is labeled for 200 doses of ipratropium bromide monohydrate at _____ µg/actuation through the mouthpiece. The proposed maximum daily recommended dose is 201.6 micrograms (6 doses or 12 inhalations). Patients are to prime the canister twice prior to taking the first dose and when the inhaler has not been used for 3 days (72 hours). Patients are advised to clean the mouthpiece

CHEMISTRY REVIEW

Executive Summary Section

at least once a week with water and dried thoroughly prior to use. Cleaning, priming and re-priming instructions are not adequately supported by data. Patients are advised to store the drug product at 25°C (77°F). Excursions between 15°C (59°F) and 30°C (86°F) are permitted.

C. Basis for Approvability or Not-Approval Recommendation

The application is recommended for an Approvable action in the current form. There are a number of critical areas related to drug product performance that need to be addressed by the applicant.

- ▶ A number of drug product acceptance criteria are not supported by the data provided. This relates to manufacturing capability, and in some cases there may be potential safety issues.
- ▶ The applicant has not provided adequate control on _____ extractables and leachables _____
- ▶ There are stability issues mainly with the product performance in terms of particle size distribution. Although formulation is stated to be a solution (based on solubility characteristics) due to significant changes in the profile of the fine particle fraction on stability, it is not clear if the formulation always remains a solution on stability. There is a significant change in the profile of the fine particle fraction over time _____ when stored at 40°C/85% RH, 30°C/75% RH, and 25°C/60% RH. These changes may result in out of specification results in APSD as measured by ACI.
- ▶ Significant amounts (_____) of foreign particulates (_____ materials) are seen in the drug product when stored inverted for _____ at 25°C/60% RH conditions. A pharm/tox consult was requested to evaluate the safety of these foreign particulates in the drug product. Dr. Whitehurst in his review recommends that although no safety concerns exist for _____ additional information pertaining to levels of _____ found in the formulation used in preclinical studies for rats be provided.
- ▶ A number of specification issues remain deficient including certain acceptance criteria, analytical procedures, and method validation.
- ▶ _____
- ▶ There is an _____ in the drug product when stored under all stability conditions. However its effect on the PSD of the drug product is not fully understood.
- ▶ The delivered dose averages out to approximately 17 µg/actuation for the primary stability batches based on release and stability. Hence a recommendation is made to change the stated labeled claim to 17µg/actuation.
- ▶ Several DMFs associated with the container closure system remain deficient.
- ▶ Comments regarding container closure system were provide to the applicant in a discipline review letter on May 6, 2003. The division is still awaiting responses to these comments.
- ▶ Labeling should be considered in the final review cycle.

III. Administrative

A. Reviewer's Signature

CHEMISTRY REVIEW

Executive Summary Section

B. Endorsement Block

Brian Rogers, Ph.D.
Prasad Peri, Ph.D.
Alan C Schroeder, Ph.D.

C. CC Block

271 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

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this page is the manifestation of the electronic signature.**

/s/

Prasad Peri
10/8/03 02:06:49 PM
CHEMIST

Brian Rogers
10/8/03 02:14:08 PM
CHEMIST

Alan Schroeder
10/8/03 02:27:46 PM
CHEMIST
Signed for Craig Bertha, Ph.D.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

DATE: Feb. 13, 2003

TO: NDA 21-527 file

FROM: Prasad Peri, Ph.D. Chemistry Reviewer, DNDC II
Division of Pulmonary and Allergy Drug Products, HFD-570

SUBJECT: Atrovent HFA (NDA21-527) filing issues identified at the time of the preliminary review.

Background

- This NDA was submitted on Dec. 2, 2002. This NDA has a history of several meetings with the company and several CMC issues were identified and communicated to the applicant.
- Two filing meetings were held to discuss CMC/Other issues within the division and Office. During the filing meetings, it was brought to the attention of the medical officers that the container closure system (specifically the valves) for the first, second and third generation products are significantly different. The second and third generation products use valve stems, which have narrower inner diameter as opposed to the first generation product. Hence the particle size distribution of the emitted dose of the second and third generation products showed a higher percentage of mass with smaller particles. From a CMC perspective the applicant had not provided data to completely link the first, second and third generation products in terms of product performance. Also to note is that the first generation product is not available any more. The pivotal clinical studies were carried out using the first generation product rather than the third generation product. The medical officers decided that these were review issues and not filing issues. It was finally decided that the NDA would be filed and comments sent to the applicant in the 74-day filing letter.

Issues/Comments

- The following preliminary CMC comments were generated to be included in the NDA filing letter. They are not all inclusive and additional issues may be identified as the review of the NDA progresses.
1. Provide Anderson Cascade Impactor (ACI) Aerodynamic Particle Size Distribution (APSD) data, including mass balance data, for all stability results from the long term, intermediate, and accelerated stability studies.
 2. Provide ACI results including an evaluation of the APSD and mass balance data from studies on for products manufactured from the second and third generation container closure system.
 3. Provide ACI results including an evaluation of the APSD and mass balance data from studies for products manufactured from the first and third generation container closure system.
 4. Design appropriate experiments to evaluate the APSD including particles, i.e., the particles that are not captured by the ACI filter. Provide such data for the first, second and third generation drug products. In addition, provide mass balance data for each of the above experiments.

**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
2/13/03 12:25:35 PM
CHEMIST

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 21527/000 Sponsor: BOEHRINGER INGELHEIM
Org Code : 570 900 RIDGEBURY RD
Priority : 3S RIDGEFIELD, CT 06877

Stamp Date : 09-DEC-2002 Brand Name : ATROVENT HFA (IPRATROPIU
PDUFA Date : 17-NOV-2004 BROMIDE) INHALAT
Action Goal : Estab. Name:
District Goal: 18-SEP-2004 Generic Name: IPRATROPIUM BROMIDE
21MCG/INHALATION
Dosage Form: (AEROSOL)
Strength : — MG/INH

FDA Contacts: L. JAFARI Project Manager (HFD-570) 301-8
7-1050
.57 P. PERI Review Chemist (HFD-570) 301-8
-5918 G. POOCHIKIAN Team Leader (HFD-800) 301-8

Overall Recommendation: ACCEPTABLE on 29-SEP-2004 by S. ADAMS (HFD-322) 3
-827-9051
ACCEPTABLE on 02-JUL-2003 by J. D AMBROGIO (HFD-32
301-827-
9049

Establishment : CFN : 2010441 FEI : 2010441
3M PHARMACEUTICALS INC
19901 NORDHOFF ST
NORTHRIDGE, CA 91328

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE OTHER TESTER

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

DMF No: _____

AADA: _____

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile : CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 31-DEC-02

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : _____ FEI : _____

DMF No: _____ AADA: _____

Responsibilities:

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 31-DEC-02

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : _____ FEI : _____

DMF No: _____ AADA: _____

