

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-527

ADMINISTRATIVE
DOCUMENTS/CORRESPONDENCE

13. PATENT INFORMATION

Required Information

(i) Applicable Patent Numbers
and Expiration Date of Each

(a) U.S. Patent No. 5,676,930
Expiration Date: June 7, 2015

(b) U.S. Patent No. 5,605,674
Expiration Date: May 31, 2015

(c) U.S. Patent No. 5,683,677
Expiration Date: May 31, 2015

(d) U.S. Patent No. 5,695,743
Expiration Date: December 9, 2014

(e) U.S. Patent No. 5,766,573
Expiration Date: November 28, 2009

(ii) Type of Patent

All above listed patents cover a drug product, i.e., all such patents have composition and formulation claims.

(iii) Name of Patent Owner

For U.S. Patent No. 5,676,930, Boehringer Ingelheim Pharmaceuticals, Inc. All other patents are owned by Riker Laboratories, Inc.

- (iv) Entity authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 C.F.R §§ 314.52 and 314.95
- For U.S. Patent No. 5,676,930, Boehringer Ingelheim Pharmaceuticals, Inc.(the applicant), which has its place of business at 900 Ridgebury Road, P.O. Box 368, Ridgefield, CT 06877. Notices concerning all other patents should be sent to General Counsel-3M Pharmaceuticals, Minnesota Mining & Manufacturing Co., whose address is 3M. Center, Building 220-11 W-02, St. Paul, MN 55144-1000.

Declaration under 21 CFR 314.53

The undersigned declares that Patent No. 5,676,930, Patent No. 5,605,074, Patent No. 5,683,677, Patent No. 5,695,743 and Patent No. 5,766,573 cover the formulation and composition of ATROVENT® HFA (ipratropium bromide) Inhalation Aerosol HFA-134a. This product is the subject of this application for approval.

By: 
Mary-Ellen M. Devlin
Title: Executive Counsel, Intellectual Property
Attorney for Applicant
Boehringer Ingelheim Pharmaceuticals, Inc.

Date: October 22, 2002

14. PATENT CERTIFICATION

Exclusivity

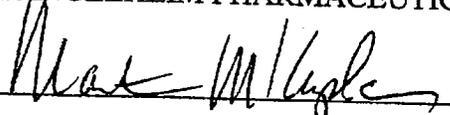
- 1) The applicant, Boehringer Ingelheim Pharmaceuticals, Inc., believes that after approval of the New Drug Application ATROVENT® HFA (ipratropium bromide) Inhalation Aerosol HFA-134a, it will be entitled to a period of marketing exclusivity under the provisions of 21 CFR 314.108, and is, therefore, claiming exclusivity.
- 2) Reference is made to 21 CFR 314.108(b)(4) to support the applicant's claim to exclusivity for ATROVENT® HFA (ipratropium bromide) Inhalation Aerosol HFA-134a.
- 3) The applicant claims exclusivity under 21 CFR 314.108(b)(4) in that:
 - (i) the New Drug Application ATROVENT® HFA (ipratropium bromide) Inhalation Aerosol HFA-134a is submitted under Section 505(b) of the Federal Food, Drug and Cosmetic Act;
 - (ii) the New Drug Application ATROVENT® HFA (ipratropium bromide) Inhalation Aerosol HFA-134a will be approved after September 24, 1984;
 - (iii) ATROVENT® HFA (ipratropium bromide) Inhalation Aerosol HFA-134a contains an active moiety (specifically ipratropium bromide) that has been previously approved in another application under Section 505(b) of the Federal Food, Drug and Cosmetic Act; and
 - (iv) the New Drug Application ATROVENT® HFA (ipratropium bromide) Inhalation Aerosol HFA-134a contains reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by Boehringer Ingelheim Pharmaceuticals, Inc., the applicant herein.

Boehringer Ingelheim
Atrovent HFA (ipratropium bromide) Inhalation Aerosol
Patent Certification

Page 2

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

By:


Martin M. Kaplan, M.D., J.D.

Title: Vice President, Drug Regulatory Affairs

Date:

Oct 22, 2002

EXCLUSIVITY SUMMARY FOR NDA # 21-527 SUPPL # _____

Trade Name Atrovent HFA Inhalation Aerosol

Generic Name ipratropium bromide HFA inhalation aerosol

Applicant Name Boehringer Ingelheim Pharmaceuticals, Inc

HFD # 570

Approval Date If Known 11-17-04

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES / X / NO / ___ /

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / X / NO / ___ /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES / / NO / /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES / / NO / /

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES / / NO / /

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / / NO / /

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

#(s).

NDA# _19-085__	Atrovent Inhalation Aerosol (CFC formulation)
NDA# _20-228	Atrovent
NDA# _20-393	Atrovent Nasal Spray
NDA 20-394	Atrovent Nasal Spray

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

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

NDA# _____	_____
NDA# _____	_____
NDA# _____	_____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / X / NO / ___ /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / X / NO / ___ /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / X / NO / ___ /

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES / ___ / NO / X /

If yes, explain:

Investigation #1-3

YES / /

NO / /

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

1. Pivotal safety & efficacy study 244.1405

2. Pivotal safety & efficacy study 244.1408

3. Safety study 244.2453

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1-3 !

IND #45,938 YES / / ! NO / / Explain: _____
!

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES / / Explain _____ ! NO / / Explain _____
!

_____ ! _____
!

Investigation #2 !

YES / / Explain _____ ! NO / / Explain _____
!

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

/s/

Badrul Chowdhury
11/17/04 02:50:48 PM

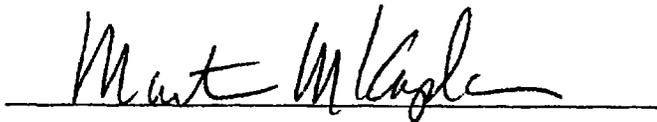
16. DEBARMENT CERTIFICATION

CERTIFICATION REQUIREMENT

SECTION 306(k)(1) OF THE ACT
21 U.S.C. 355a(k)(1)

Boehringer Ingelheim Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) [Section 306(a) or (b)] of the Federal Food, Drug and Cosmetic Act in connection with ATROVENT® HFA (ipratropium bromide) Inhalation Aerosol.

Signature:



Name of the Applicant:

Martin Kaplan, M.D., J.D.
Vice President, Drug Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.

Date:

October 22, 2002

Mailing Address:

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # 21-527: _____ Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: Original :December 9, 2002, Resubmission: May 17, 2004 _____ Action Date: November 17, 2004

HFD 570 Trade and generic names/dosage form: Atrovent HFA (ipratropium bromide) Inhalation Aerosol

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI)

Therapeutic Class: Respiratory

Indication(s) previously approved: N/A

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Bronchospasm associated with chronic Obstructive Pulmonary Disease

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-527
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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

/s/

Ladan Jafari

6/7/04 01:59:43 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information

NDA 21-527	Efficacy Supplement Type SE-	Supplement Number
Drug: Atrovent HFA (ipratropium bromide HFA) Inhalation Aerosol		Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.
RPM: Ladan Jafari		HFD-570 Phone #301-827-1084
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed and/or corrected</p>		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):
❖ Application Classifications:		
<ul style="list-style-type: none"> • Review priority 		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
<ul style="list-style-type: none"> • Chem class (NDAs only) 		3
<ul style="list-style-type: none"> • Other (e.g., orphan, OTC) 		N/A
❖ User Fee Goal Dates		November 17, 2004
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
<ul style="list-style-type: none"> • User Fee 		<input checked="" type="checkbox"/> Paid UF ID number 4445
<ul style="list-style-type: none"> • User Fee waiver 		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)
<ul style="list-style-type: none"> • User Fee exception 		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)
❖ Application Integrity Policy (AIP)		
<ul style="list-style-type: none"> • Applicant is on the AIP 		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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

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

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

Yes No

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

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

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

Yes No

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

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

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> Exclusivity summary Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	See Attached/11-17-04
<ul style="list-style-type: none"> Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	<input type="checkbox"/> Yes, Application # _____ <input type="checkbox"/> No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	May 2, 2003

General Information

General Information	
Actions	
• Proposed action	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA
• Previous actions (specify type and date for each action taken)	AE/October 9, 2003
• Status of advertising (approvals only)	<input checked="" type="checkbox"/> Materials requested in AP letter <input type="checkbox"/> Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> Not applicable
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input type="checkbox"/> Press Release <input type="checkbox"/> Talk Paper <input type="checkbox"/> Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	November 10, 2004
• Most recent applicant-proposed labeling	November 12, 2004
• Original applicant-proposed labeling	December 6, 2002
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (<i>indicate dates of reviews and meetings</i>)	See attached.
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	November 10, 2004
• Applicant proposed	November 12, 2004
• Reviews	See CMC review
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	
	See Attached
❖ Memoranda and Telecons	
	See Attached
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	May 26, 2000
• Pre-NDA meeting (indicate date)	January 16, 2002, March 27, 2002
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
	N/A

Summary Application Review

Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader)
(indicate date for each review)

October 9, 2003, September 30,
2003, November 17, 2004

Clinical Information

❖ Clinical review(s) (indicate date for each review)	September 25, 2003
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	October 12, 2004
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	See attached
❖ Demographic Worksheet (NME approvals only)	N/A
❖ Statistical review(s) (indicate date for each review)	September 22, 2003
❖ Biopharmaceutical review(s) (indicate date for each review)	September 24, 2003, February 5, 2003
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A

CMC Information

❖ CMC review(s) (indicate date for each review)	Nov. 15, 2004, June 9, 2004, October 8, 2003
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	Nov. 15, 2004
• Review & FONSI (indicate date of review)	N/A
• Review & Environmental Impact Statement (indicate date of each review)	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	N/A
❖ Facilities inspection (provide EER report)	Date completed: September 29, 2004 (X) Acceptable () Withhold recommendation
❖ Methods validation	() Completed () Requested (X) Not yet requested

Nonclinical Pharm/Tox Information

❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	September 1, 2004, October 2, 2003
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A



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

FACSIMILE TRANSMITTAL SHEET

DATE: November 17,2004

To: George Chen	From: Ladan Jafari
Company: BIPI	Division of Pulmonary and Allergy Drug Products
Fax number: 203-791-6262	Fax number: 301-827-1271
Phone number: 203-798-4942	Phone number: 301-827-1084

Subject: NDA 21-527

Total no. of pages including cover: 7

Comments: labeling comments

Document to be mailed: YES NO

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NDA 21-527

Drug: Atrovent HFA

Applicant: BIPI

Dates of telecon: October 27, and 29, 2004

BIPI Representatives:

Terrence Tougas, CMC Expert
Dennis O'Connor, TM Analytical Sciences
Paul Jager, TM Pharmaceutical Sciences
Dan Norwood, Analytical Sciences
Gordon Hansen, Analytical Sciences
Julius Funari, TM Operations
George Chen, Technical DRA
Jeff Snyder, Regulatory Affairs

Division of Pulmonary & Allergy Drug Products (DPADP) Representatives:

Prasad Peri, Ph.D., CMC Reviewer
Richard Lostritto, Ph.D., CMC Team Leader
Ladan Jafari, Regulatory Project Manager
Alan Schroeder, Ph.D., CMC Reviewer*
Virgil Whitehurst, Ph.D., Preclinical Reviewer*
Timothy McGovern, Ph.D., Preclinical Supervisor*

*Asterisk denotes that these individuals were also present at the telecon dated October 29, 2004.

Background: The Division sent a telephone facsimile dated October 22, 2004, to BIPI and arranged for a telephone conference to discuss the issues identified in this telephone facsimile. The content of this correspondence is printed in *Italics* below. BIPI submitted a response to this correspondence dated October 26, 2004. Any discussions relevant to these issues are printed in regular font directly under each item.

The following comments pertain to Report U04-3190.

1. *Provide an explanation for the following observation from your report U04-3190: The results indicate that the leachable — (see figure 4) is observed in the drug product at a higher concentration than the —. Justify the conditions used for the — drug product leachables testing.*
- The Division acknowledged BIPI's response dated October 26, 2004, and stated that the acceptability of the data would be a review issue.

NDA 21-527

Drug: Atrovent HFA

Applicant: BIPI

Dates of telecon: October 27, and 29, 2004

Page 2

2. *Your current proposed _____ specifications are not considered safe. Since _____ have not been observed in the data to date, tighten the acceptance criteria for individual _____, e.g., not more than _____ and propose a limit on total _____, e.g., not more than _____.*
Revise the leachable specifications to list individual _____ with appropriate acceptance criteria (e.g., _____).
- The Division stated that presence of _____ is undesirable, however, we agree with BIPI's proposal dated October 26, 2004, and accept the limits proposed.
- With regard to the presence of _____, the Division stated that based upon the data provided by BIPI dated October 26, 2004, we could agree to a specification of _____ for individual _____ and a total specification of _____.
 - BIPI indicated that they would discuss it internally and inform the Division of their decision.

Post-Meeting notes:

BIPI submitted a response dated October 29, 2004, and agreed to limit the specifications for the individual _____ to _____, and total specification to _____.

3. *Incorporate mass balance (MB) into your aerodynamic particle size distribution (APSD) test method and specification (e.g., _____) as a regulatory criterion, not as a run qualification.*
- The Division agreed with BIPI's response dated October 26, 2004.
4. *Revise the acceptance limits for the following APSD stage groupings as measured by cascade impactor to be representative of the data provided. _____*
- The Division did not agree with BIPI's proposal and suggested that BIPI adopt an interim specifications for the Aerodynamic Particle Size Distribution test that would limit the specifications to _____.
 - BIPI indicated that they would discuss this suggestion internally and inform the Division of their decision.

NDA 21-527

Drug: Atrovent HFA

Applicant: BIPI

Dates of telecon: October 27, and 29, 2004

Page 3

Post-Meeting notes:

BIPI submitted a response dated October 29, 2004, and agreed with the Division's recommendation above for

5. *Institute spray pattern testing as part of the regulatory specifications. When a significant body of data becomes available from the marketed drug product, a proposal to significantly reduce the frequency of this test may be made along with suitable justification and data in a prior approval supplement.*
- The Division acknowledged BIPI's response dated October 26, 2004, and stated that we would honor the advice given at the Pre-NDA CMC meeting dated March 27, 2002 (meeting minutes dated May 1, 2002). This would be further addressed post-approval.
6. *Clarify your sampling plan for the incoming mouthpieces used in the Atrovent HFA Inhalation Aerosol drug product. Indicate what actions will be taken to eliminate non-conforming mouthpieces received from the mouthpiece manufacturer.*
- The Division acknowledges BIPI's response dated October 29 2004. This response is currently under review.
7. *Provide the levels of all leachables observed from the stressed samples and their relationship to the drug product samples observed at the end of shelf life.*
- The Division acknowledged BIPI's response dated October 26, 2004, and stated that the decision regarding the acceptability of the data would be a review issue.
8. *Provide an agreement to identify and quantitate the leachable*
- The Division acknowledges BIPI's response dated October 29 2004. This response is currently under review.
9. *Provide leachables data for the*
- The Division acknowledges BIPI's response dated October 29 2004. This response is currently under review.
10. *As requested previously, incorporate into the method, the relative response factors for all the impurities that are to be quantified by method*

NDA 21-527

Drug: Atrovent HFA

Applicant: BIPI

Dates of telecon: October 27, and 29, 2004

Page 4

- The Division acknowledges BIPI's response dated October 29 2004. This response is currently under review.

11. *Clarify the difference in the rejection numbers for lot 980984 as provided in tables 5.1 and 5.2. The Agency acknowledges your agreement to provide the results of the checkweighing rejection rates to the Division on the first commercial batches in the Annual report as they become available.*

- The Division acknowledges BIPI's response dated October 29 2004. This response is currently under review.

12. *Provide the actual results for the _____ used in the manufacture of the primary stability batches.*

- The Division acknowledges BIPI's response dated October 29 2004. This response is currently under review.

13. *Clarify the following discrepancy: _____*

/

- The Division acknowledges BIPI's response dated October 29 2004. This response is currently under review.

14.

/

- The Division acknowledges BIPI's response dated October 29 2004. This response is currently under review.

NDA 21-527

Drug: Atrovent HFA

Applicant: BIPI

Dates of telecon: October 27, and 29, 2004

Page 5

15. *Clarify the discrepancy in the leachables levels observed in the primary stability lots (000103, 000104, and 000105) when stored at 30/70% RH. Table 4.1.1:3 R on pages 174 and 175 of the May '14, 2004, submission differs in the leachable values for lot 000104 presented in Table 2.18:1 on page 126, of volume 8 of the original submission. Indicate whether the data presented in Table 2.18:1 on page 126, of volume 8 include results from the upright canisters.*

- The Division acknowledges BIPI's response dated October 29 2004. This response is currently under review.

The Division asked that BIPI clarify the difference in LOQ for the _____
_____ for Aluminum cans used with _____ Atrovent HFA.

The Division also suggested that BIPI institute a leachable specification for _____
in the drug product. BIPI stated that they do not have a validated method for this and suggested that it would have to be a post approval agreement. The Division suggested that they validate a method and institute a specification for _____ as a leachable in the drug product, within _____ after approval of the drug product.

The Division also sent the following comments via a telephone facsimile, dated October 28, 2004, and arranged a second teleconference to discuss this correspondence. The content of this correspondence is also printed in Italics below. All discussions relevant to this correspondence are printed in regular font directly under each point.

*The proposed specification for leachable, with regard to _____ is too high. _____
_____. You may do one of the following to address
this issue:*

1. *Lower the specification to NMT _____ /canister.*
2. *Lower the specifications to NMT _____ /canister and provide the results of a 90 day animal qualification study for our review within nine months post approval. We recommend that you provide the protocol for your proposed animal qualification study for the Division's feedback within two months post-approval.*
3. *Lower the specifications to NMT _____ /canister and provide published literature to support your proposed specification and/or provide information about a marketed MDI drug product similar to Atrovent HFA Inhalation solution that contains this leachable. In addition, provide the details of the proposed qualification within two months post approval. Please note that the decision on the adequacy of the data obtained from published literature or from another MDI, is a review issue.*

4. Lower the specifications to NMT _____ canister and if available, provide the actual levels of _____ in the drug formulation given to the rats in the 90 day study with Atrovent HFA to allow for an adequate safety assessment within two months post-approval.

- The Division explained that in order to use the completed 90-day rat study to qualify _____ for safety, we need the actual levels of _____ in the administered formulation at the time of dosing in order to determine the exposure levels in the rats. The data provided with the NDA submission are inadequate to qualify the safety of this impurity since the reported levels are likely higher than those administered to the rats. The Division reiterated that the specification for _____ must be lowered to NMT _____ canister. The Division also suggested that BIPI lower the shelf life for Atrovent HFA to 18 months until additional toxicology studies are provided to allow a maximum of _____ shelf life.
- The Division acknowledges BIPI's response dated October 29 2004. This response is currently under review.

In addition to the above, the Division discussed the following CMC issues.

- The Division explained that since Atrovent HFA would be the first stainless steel canister approved, _____ BIPI should provide a specification for _____ in the stability studies post-approval. This frequency of testing may be reduced once adequate data on commercial lots are generated.
- The Division stated that BIPI should revise the acceptance criteria for _____ to reflect the data provided. The proposed limits are still not representative of the data.
- The Division asked that BIPI institute acceptance criteria for _____ material. BIPI indicated that they do not have acceptance criteria at this point, but would work with _____ to provide this information. BIPI also stated that the acceptance limit would be more appropriate for _____ to institute at a component level. The Division suggested that in the interest of time, it would be easier for BIPI to set this limit.
- The Division reminded BIPI that any information requested for post-approval should be submitted as "prior approval supplement".

NDA 21-527

Drug: Atrovent HFA

Applicant: BIPI

Dates of telecon: October 27, and 29, 2004

Page 7

Drafted by: LJ/11-4-04

Initialed by: Peri/11-8-04

Schroeder/11-15-04

Whitehurst/11-8-04

McGovern/11-8-04

Lostritto/11-8-04

Filename: N21527tconmin.doc

NDA 21-527

Date of telecon: November 17, 2004

I spoke with Jeff Snyder and Pat Watson of BIPI to ask for their agreement to modify the following agreements. Those agreed upon changes are shown as track changes. Both Jeff Snyder and Pat Watson agreed with these modifications.

1. Within 12 months of approval of the application, propose tightened acceptance criteria for the _____ test in the drug product specification on the basis of standard process capability analysis (i.e., using the standard criterion of a process capability index, $C_{PK}=1.3$). As noted in the CMC Amendment 014, you may also propose _____ via a prior approval supplement once a sufficient body of data has been accumulated to justify its removal from the specification.

2. Within 12 months of approval of the application. _____

3. Within six months of approval of the application, the specification for the canister will be revised to control _____

_____ The revised acceptance criteria for the specification

4. It is our expectation that in accordance with CDER's Guidance to Industry on Dose Counters, Atrovent HFA (ipratropium bromide HFA) Inhalation Aerosol will have a dose-indicating device. Provide a prior approval supplement to incorporate the dose actuation indicator for Atrovent HFA (ipratropium bromide HFA) Inhalation Aerosol within _____

Ladan Jafari
Regulatory Project Manager

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/s/

Ladan Jafari
11/17/04 03:52:46 PM
CSO



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

FACSIMILE TRANSMITTAL SHEET

DATE: November 8, 2004

To: Jeff Snyder	From: Ladan Jafari
Company: BIPI	Division of Pulmonary and Allergy Drug Products
Fax number: 203-837-4928	Fax number: 301-827-1271
Phone number: 203-778-7727	Phone number: 301-827-1084
Subject: NDA 21-527	
Total no. of pages including cover: 2	

Comments: CMC Comments

Document to be mailed: YES NO

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Dear Dr. Chen:

We are reviewing your NDA for Atrovent HFA and ask that you provide your agreement to the following revisions by COB Wednesday November 10, 2004.

1. Name a testing laboratory that will perform the _____ testing within 12 months of approval of the application _____
2. Revise the stability protocol to include testing for _____ the drug product and to analyze for trends in the commercial lots of drug product. Provide updated specification sheets and a revised stability protocol within 1 month of the approval of the application.
3. Agree to provide the identities for the components of the individual constituents using standard chemical nomenclature or other terminology that will allow for the determination of the chemical structures for the components _____ within 3 months of the approval of the application.
4. The proposed acceptance criteria for spray pattern testing are well outside the current state of the art and are not supported by your data. We ask that that you agree to propose tighter acceptance limits which are based on and reflective of the data within 12 months of approval. Provide the appropriately updated specification sheet at the same time.
5. The shelf life may not be extended via annual reports. Provide proposals for shelf life extensions via a prior approval supplement with sufficient and appropriate relevant (leachables, foreign particulate matter, etc.) data.
6. Agree to institute a leachable specification for _____ in the drug product within 12 months of approval of the application.
7. Revise the specification for the control of _____ Provide updated specification sheets and a revised stability protocol within 1 month of the approval of the application.

I may be reached at 301-827-1084 for any questions.

Ladan Jafari, Regulatory Project Manager

Initialed by: Barnes/11-8-04
Peri/11-8-04
Schroeder/11-8-04
Bertha for Lostritto/11-8-04

Filename: N215272ndCMCcomments

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Ladan Jafari
11/8/04 12:19:17 PM
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Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: November 10,2004

To: Jeff Snyder	From: Ladan Jafari
Company: BIPI	Division of Pulmonary and Allergy Drug Products
Fax number: 203-837-4928	Fax number: 301-827-1271
Phone number: 203-778-7727	Phone number: 301-827-1084

Subject: NDA 21-527

Total no. of pages including cover: 21

Comments: labeling comments

Document to be mailed: *Yes* *No*

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§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

9 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

 § 552(b)(4) Draft Labeling



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

FACSIMILE TRANSMITTAL SHEET

DATE: October 28, 2004

To: George Chen	From: Ladan Jafari
Company: BIPI	Division of Pulmonary and Allergy Drug Products
Fax number: 203-791-6262	Fax number: 301-827-1271
Phone number: 203-798-4942	Phone number: 301-827-1084

Subject: NDA 21-527

Total no. of pages including cover: 3

Comments: CMC/Preclinical comments

Document to be mailed: *Yes* *No*

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NDA 21-527

Dear Dr. Chen:

In response to the questions raised at the teleconference held on October 27, 2004, we have the following clarifying information:

- Your assumption is correct that we were referring to Combivent CFC and Atrovent HFA for the inconsistency in the LOQ for _____ method.
- The acceptance criteria for _____ NMT _____, total _____ NMT _____ are acceptable.
- We are still evaluating the meeting minutes dated May 1, 2002, for the Spray Pattern Testing. This issue will be discussed in the upcoming teleconference scheduled for October 29, 2004.

We also have the following additional request for information.

The proposed specification for leachable, with regard to _____ is too high _____. You may do one of the following to address this issue:

1. Lower the specification to NMT _____ /canister.
2. Lower the specifications to NMT _____ canister and provide the results of a 90 day animal qualification study for our review within nine months post approval. We recommend that you provide the protocol for your proposed animal qualification study for the Division's feedback within two months post-approval.
3. Lower the specifications to NMT _____ /canister and provide published literature to support your proposed specification and/or provide information about a marketed MDI drug product similar to Atrovent HFA Inhalation solution that contains this leachable. In addition, provide the details of the proposed qualification within two months post approval. Please note that the decision on the adequacy of the data obtained from published literature or from another MDI, is a review issue.
4. Lower the specifications to NMT _____ canister and if available, provide the actual levels of _____ in the drug formulation given to the rats in the 90 day study with Atrovent HFA to allow for an adequate safety assessment within two months post-approval.

The above comments are not all inclusive as we are still evaluating the proposed drug product specifications for the extractables/leachables.

N 21-527

Page 2

I may be reached at 301-827-1084 for any questions.

Ladan Jafari, Regulatory Project Manager

N 21-527

Page 3

Drafted by: LJ/10-28-04

Initialed by: Barnes/10-28-04
Peri/10-28-04
Lostritto/10-28-04
Schroeder/10-28-04
Whitehurst/10-28-04
McGovern/10-28-04

Filename: N21527comments

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Ladan Jafari
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Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: October 22, 2004

To: George Chen	From: Ladan Jafari
Company: BIPI	Division of Pulmonary and Allergy Drug Products
Fax number: 203-791-6262	Fax number: 301-827-1271
Phone number: 203-798-4942	Phone number: 301-827-1084

Subject: NDA 21-527

Total no. of pages including cover: 3

Comments: CMC Comments

Document to be mailed: YES NO

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Dear Dr. Chen:

We are reviewing your resubmission dated May 14, 2004, and we have the following comments and requests for information. We ask that you provide responses to these requests by Friday October 29, 2004. These comments are not necessarily all inclusive.

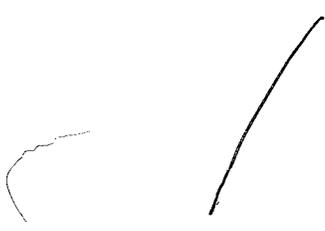
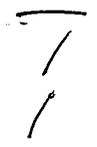
The following comments pertain to Report U04-3190.

1. Provide an explanation for the following observation from your report U04-3190:

2. Your current proposed _____ specifications are not considered safe. Since _____ have not been observed in the data to date, tighten the acceptance criteria for individual _____ and propose a limit on total _____. (_____.). Revise the leachable specifications to list individual _____ with appropriate acceptance criteria (e.g., _____).
3. Incorporate mass balance (MB) into your aerodynamic particle size distribution (APSD) test method and specification (e.g., _____, as a regulatory criterion, not as a run qualification).
4. Revise the acceptance limits for the following APSD stage groupings as measured by cascade impactor to be representative of the data provided.
5. Institute spray pattern testing as part of the regulatory specifications. When a significant body of data becomes available from the marketed drug product, a proposal to significantly reduce the frequency of this test may be made along with suitable justification and data in a prior approval supplement.
6. Clarify your sampling plan for the incoming mouthpieces used in the Atrovent HFA Inhalation Aerosol drug product. Indicate what actions will be taken to eliminate non-conforming mouthpieces received from the mouthpiece manufacturer.

We also have the following requests for information and ask that you provide your agreements to perform the following within 12 months of the approval of the application.

7. Provide the levels of all leachables observed from the stressed samples and their relationship to the drug product samples observed at the end of shelf life.

8. Provide an agreement to identify and quantitate the leachable . —
9. Provide leachables data for the —
10. As requested previously, incorporate into the method, the relative response factors for all the impurities that are to be quantified by method —
11. Clarify the difference in the rejection numbers for lot 980984 as provided in tables 5.1 and 5.2. The Agency acknowledges your agreement to provide the results of the checkweighing rejection rates to the Division on the first — commercial batches in the Annual report as they become available.
12. Provide the actual results for the — used in the manufacture of the primary stability batches.
13. Clarify the following discrepancy: —

14. For the method —


15. Clarify the discrepancy in the leachables levels observed in the primary stability lots (000103, 000104, and 000105) when stored at 30/70% RH. Table 4.1.1:3 R on pages 174 and 175 of the May 14, 2004, submission differs in the leachable values for lot 000104 presented in Table 2.18:1 on page 126, of volume 8 of the original submission. Indicate whether the data presented in Table 2.18:1 on page 126, of volume 8 include results from the upright canisters.

Additional labeling (storage orientation of the drug product) and DMF related comments may be forthcoming.

If you have any questions, I may be reached at 301-827-1084.

NDA 21-527

Page 3

Initialed by: Barnes/10-22-04
Peri/10-22-04
Schroeder/10-22-04
Lostritto/10-22-04

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Ladan Jafari
10/22/04 01:27:03 PM
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FACSIMILE TRANSMITTAL SHEET

DATE: September 14, 2004

To: Jeffrey Snyder	From: Ladan Jafari
Company: BIPI	Division of Pulmonary and Allergy Drug Products
Fax number: 203-778-7357	Fax number: 301-827-1271
Phone number: 203-778-7727	Phone number: 301-827-1084

Subject: NDA 21-527

Total no. of pages including cover: 20

Comments: labeling Comments

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Dear Mr. Snyder:

Attached please find a copy of the labeling for Atrovent HFA with changes marked. We may provide additional labeling comments as the review of this NDA progresses.

I may be reached at 301-827-1084 for any questions.

Ladan Jafari, Regulatory Project Manager

Initialed by: Barnes/9-13-04
Gilbert-McClain/9-13-04
Chowdhury/9-14-04

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§ 552(b)(5) Deliberative Process

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/s/

Ladan Jafari
9/14/04 02:44:12 PM
CSO

Ladan Jafari
9/14/04 02:52:18 PM
CSO

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)**

DATE RECEIVED: 6/7/04

DESIRED COMPLETION DATE: 10/29/04

ODS CONSULT #: 04-0170

TO: Badrul Chowdhury, MD
Director, Division of Pulmonary and Allergy Drug Products
HFD-750

THROUGH: Ladan Jafari
Project Manager
HFD-570

PRODUCT NAME:
Atrovent® HFA
(Ipratropium Bromide) Inhalation Aerosol
17 mcg/actuation

NDA SPONSOR: Boehringer Ingelheim

NDA #: 21-527

SAFETY EVALUATOR: Felicia Duffy, RN

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Atrovent HFA. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document
2. DMETS recommends implementation of the labeling revisions outlined in section III of this review in order to minimize potential errors with the use of this product.
3. DDMAC finds the proprietary name Atrovent HFA acceptable from a promotional perspective

Carol Holquist, RPh
Director, Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

**Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: July 15, 2004

NDA # 21-527

NAME OF DRUG: Atrovent® HFA
(Ipratropium Bromide) Inhalation Aerosol
17 mcg/actuation

NDA HOLDER: Boehringer Ingelheim

I. INTRODUCTION:

This consult was written in response to a request from the Division of Pulmonary and Allergy Drug Products (HFD-570), for assessment of the proprietary name, "Atrovent HFA", regarding potential name confusion with other proprietary or established drug names. The insert labeling was provided for review and comment.

Atrovent Inhalation Aerosol (NDA 19-085) is a metered-dose inhaler that was approved on December 29, 1986. Atrovent contains chlorofluorocarbons (CFCs) as a propellant. Atrovent HFA does not contain CFCs and will replace Atrovent once it is approved.

PRODUCT INFORMATION

Atrovent HFA Inhalation Aerosol is a pressurized metered-dose aerosol unit for oral inhalation that contains the active ingredient ipratropium bromide. It is indicated as a bronchodilator for the maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema. Atrovent HFA will be available in a 12.9 g canister that yields 200 inhalations. Each actuation of Atrovent HFA will deliver 21 mcg of Ipratropium bromide from the valve and 17 mcg from the mouthpiece. The usual starting dose is two inhalations four times a day.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2}, as well as several FDA databases³ for existing drug names which sound-alike or

¹ MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.

look-alike to Atrovent HFA to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁴. The Saegis⁵ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Atrovent HFA. Potential concerns regarding drug marketing and promotion related to the proposed name was also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name Atrovent HFA acceptable from a promotional perspective.
2. The Expert Panel identified two proprietary names that were thought to have the potential for confusion with Atrovent HFA. These products are listed in table 1 (see below), along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other**
Atrovent HFA	Ipratropium Bromide Inhalation Aerosol: 17 mcg/inhalation	2 inhalations QID.	
Atrovent	Ipratropium Bromide Metered-dose Inhaler: 18 mcg/inhalation Inhalation Solution: 0.02% Nasal Spray: 0.03% and 0.06%	<u>Metered-dose inhaler:</u> 2 inhalations BID <u>Inhalation solution:</u> 500 mcg (1 unit dose) TID-QID by oral nebulizer. <u>Nasal Spray:</u> 0.03%= 2 sprays/nostril BID-TID 0.06%= 2 sprays/nostril TID-QID	SA/LA
Flovent HFA	Fluticasone Propionate Inhalation Aerosol: 44 mcg/inhalation, 110 mcg/inhalation, and 220 mcg/inhalation	Previously on bronchodilators alone: initially 88 mcg twice daily; max 440 mcg twice daily. Previously on inhaled corticosteroids: initially 88-220 mcg twice daily; max 440 mcg twice daily, Previously on oral corticosteroids: 880 mcg twice daily.	LA
*Frequently used, not all-inclusive. **LA (look-alike), SA (sound-alike)			

⁴ WWW location <http://www.uspto.gov/tmdb/index.html>.

⁵ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

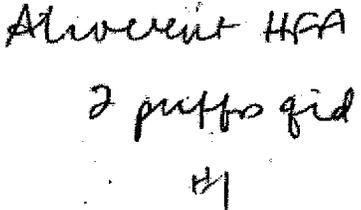
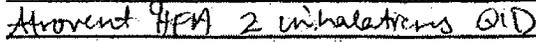
B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Atrovent HFA were discussed by the Expert Panel (EPD).

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Atrovent HFA with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 123 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Atrovent HFA (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p><u>Outpatient RX:</u></p> 	<p>Atrovent HFA 2 puffs qid Dispense 1</p>
<p><u>Inpatient RX:</u></p> 	

2. Results:

It is noted that one of the respondents from the verbal prescription study omitted the modifier HFA, misinterpreting the name as Atrovent, a currently marketed drug product. Additionally, the modifier was misinterpreted as "HAS" and "HSA". None of the other interpretations of the

proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See appendix A for the complete listing of interpretations from the verbal and written studies.

D. Adverse Event Reporting System (AERS) and Drug Quality Reporting System (DQRS) SEARCH

Atrovent has been marketed since 1986, thus DMETS searched the FDA Adverse Events Reporting System (AERS) database and the Drug Quality Report System (DQRS) to determine any post-marketing safety reports of medication errors associated with Atrovent. The MedDRA Preferred Term (PT), "Medication Error" and tradename "Atrovent" and "Ipratropium Bromide" were used to perform the searches. This search strategy retrieved sixty-eight (68) medication errors. Fifty-five (55) cases were the result of similar appearing labeling and packaging of the Atrovent inhalation solution with the following LDPE inhalation solution products: AccuNeb, Albuterol, DuoNeb, Intal, Pulmozyme, Sodium Chloride, and Xopenex. DMETS has conducted a post-marketing review concerning the issue of confusion with LDPE vials (see ODS consult #02-0048). DMETS will continue to monitor the potential for confusion with LDPE products. Eleven reports (11) related to the incorrect route of administration of Atrovent. Six (6) of the eleven cases reported Atrovent inhalation solution was administered intravenously and four (4) cases reported Atrovent nasal spray ordered, however, Atrovent inhalation aerosol was dispensed. The causality for the oral inhalation vs. nasal spray was noted as order entry error and the infrequent use of Atrovent nasal spray whereas Atrovent oral inhalation aerosol was dispensed. The last case (1) reported Atrovent inhalation solution was administered via the tracheal tube. Two (2) AERS reports were related to Atrovent inhalers. One case resulted in a prescription for Atrovent inhaler being filled with a Proventil inhaler. No causality was noted for the error. The other case resulted in the dispensing of an Atrovent inhaler instead of an Alupent inhaler. No causality was given for the error, however, the two products may have been stored side by side on the pharmacy shelf and the result could be a miss-pull. No reported errors were related to name confusion. An AERS search was also performed to determine any post-marketing safety reports of medication errors associated between HFA containing products (Proventil HFA, Ventolin HFA, Flovent HFA, and Nasacort HFA) and between HFA products and their CFC containing product (Proventil/Proventil HFA, Ventolin/Ventolin HFA, Flovent/Flovent HFA, and Nasacort/Nasacort HFA). No errors were reported between the HFA containing product and its CFC containing counterpart.

E. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Atrovent HFA, the primary concerns related to look-alike and sound-alike confusion with Atrovent and Flovent HFA. Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that the proposed name could be confused with Atrovent, because one respondent from the verbal prescription study omitted the modifier HFA. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Atrovent HFA. Additionally, there are four drug products that are currently available with the HFA modifier: Proventil HFA, Ventolin HFA, Flovent HFA and Nasacort HFA. To date, there has been no confusion with the HFA modifier.

1. Atrovent contains ipratropium bromide and is available in three formulations. The strength of the metered-dose aerosol inhaler is 18 mcg/actuation, the solution for inhalation strength is 0.02%, and as a nasal spray strengths are 0.03% and 0.06%. Atrovent is indicated for the maintenance of treatment of bronchospasm associated with chronic obstructive pulmonary

disease (solution and aerosol) and for rhinorrhea (nasal spray). Atrovent HFA will be the CFC free replacement product for Atrovent. The usual dose for the metered-dose aerosol inhaler is two inhalations four times a day. The dose for the inhalation solution is 500 mcg (1 unit dose) three to four times daily via oral nebulizer, and the nasal spray dose is two sprays/nostril two to four times daily. Atrovent and Atrovent HFA sound and look similar because they share the same root name, Atrovent. The only difference between the two products is the modifier "HFA". Both products share the same active ingredient, indication for use, usual dosage, frequency of administration, route of administration, and dosage form. Although Atrovent HFA is the replacement product for Atrovent, Atrovent delivers 18 mcg/actuation, whereas Atrovent HFA delivers 17 mcg/actuation. Atrovent HFA is the replacement product for Atrovent. Atrovent will no longer be manufactured once the HFA product is approved. There may be period of overlap where Atrovent and Atrovent HFA are available at the same time. It is likely that these products will be stored in close proximity until Atrovent has been completely removed from the shelf. This has the potential to cause a medication error when one is in a busy clinic, pharmacy or inpatient unit where the wrong product can be dispensed. If errors occur between Atrovent HFA and Atrovent, patient harm will not be an issue because the patient will receive the same product in a different formulation. DMETS believes that the potential for confusion between the two formulations of Atrovent HFA and Atrovent is limited due to the fact that the two formulations will coincide for a short period of time ([] — []), during the initial product launch.

2. Flovent HFA may look similar to Atrovent HFA when scripted. Flovent HFA is a metered-dose inhaler indicated for the maintenance treatment of chronic asthma. The active ingredient of Flovent HFA is fluticasone propionate. It is available in the following strengths: 44 mcg/inhalation, 110 mcg/inhalation, and 220 mcg/inhalation. The usual dose is 88 mcg to 880 mcg twice daily. Flovent HFA and Atrovent HFA may look similar because they share the same ending ("vent") and modifier ("HFA"). The letter "F" can look similar to the letter "A" when scripted. The letter "r" in Atrovent helps to differentiate it from the word Flovent. Both drug products share a similar indication for use (maintenance treatment of chronic asthma vs. maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease). Flovent HFA and Atrovent HFA are both also metered-dose inhalers administered orally. Each product can be prescribed with the same dosing directions "take 2 puffs" or "take 2 inhalations". Although these products have some similarities, their differences include strength (44 mcg/inhalation, 110 mcg/inhalation, and 220 mcg/inhalation vs. 17 mcg/inhalation) and frequency of administration (twice daily vs. four times daily). In addition, since Flovent HFA is available in multiple strengths, the strength must be noted on a prescription. Atrovent HFA will be available in one strength, so the strength may be omitted on a prescription. Additionally, to date there have not been any reported cases of errors between Flovent HFA and Atrovent or Flovent and Atrovent. Overall, based on differentiating product characteristics and post marketing surveillance, DMETS believes that the potential for confusion between Flovent HFA and Atrovent HFA is minimal.

Flovent HFA

Atrovent HFA

Flovent HFA

Atrovent HFA

C

 1 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling



IV. RECOMMENDATIONS:

- A. DMETS has no objections to the use of the proprietary name Atrovent HFA. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.
- B. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.
- C. DDMAC finds the proprietary name Atrovent HFA acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

Felicia Duffy, RN
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, RPh
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Appendix A. Atrovent HFA Prescription Study Results

Written Inpatient	Written Outpatient	Verbal
Atrovent HFA	Aliverent HFA	Atrovent
Atrovent HFA	Ativirent HFA	Atrovent HAS
Atrovent HFA	Atrovent HFA	Atrovent HFA
Atrovent HFA	Atrovent HFA	Atrovent HFA
Atrovent HFA	Atrovent HFA	Atrovent HFA
Atrovent HFA	Atrovent HFA	Atrovent HFA
Atrovent HFA	Atrovent HFA	Atrovent HFA
Atrovent HFA	Atrovent HFA	Atrovent HFA
Atrovent HFA	Atrovent HFA	Atrovent HFA
Atrovent HFA	Atrovent HFA	Atrovent HFA
Atrovent HFA	Atrovent HFA	Atrovent HFA
Atrovent HFA	Atrovent HFA	Atrovent hfa
Atrovent HFA	Atrovent HFA	Atrovent HFA
Atrovent HFA	Atrovent HFA	Atrovent HFA
Atrovent HFA		Atrovent HSA
Atrovent HFA		Atrovent HSA

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/s/

Felicia Duffy
9/3/04 08:37:24 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
9/3/04 12:29:23 PM
DRUG SAFETY OFFICE REVIEWER



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

FACSIMILE TRANSMITTAL SHEET

DATE: June 2, 2004

To: George Chen	From: Ladan Jafari
Company: BIPI	Division of Pulmonary and Allergy Drug Products
Fax number: 203-791-6262	Fax number: 301-827-1271
Phone number: 203-798-4942	Phone number: 301-827-1084

Subject: NDA 21-527

Total no. of pages including cover: 2

Comments: CMC comments

Document to be mailed: • YES NO

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NDA 21-527

Dear Dr. Chen:

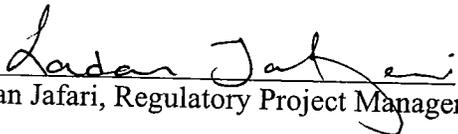
We have reviewed your correspondence dated April 28, 2004, which pertains to your proposal for post-approval agreements for development and implementation of drug product specifications for — leachables. We have the following comments.

Your proposals are acceptable, with the following changes to the proposed stability protocol (page 3 of the April 28, 2004, letter):

Add an — time-point.

Note that the final specification for — leachables should be based on data no older than the expiration dating period for the approved product.

If you have any questions, I may be reached at 301-827-1084.


Ladan Jafari, Regulatory Project Manager

NDA 21-527

Page 2

Initialed by: Barnes
Schroeder
Lostritto

Filename: N21527CMC comments

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/s/

Ladan Jafari
6/2/04 02:31:30 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-527

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P. O. Box 368
Ridgefield, CT 06877-0368

Attention: Jeffrey R. Snyder
Senior Associate Director

Dear Mr. Snyder:

We acknowledge receipt on May 17, 2004, of your May 14, 2004, resubmission to your new drug application for Atrovent HFA (ipratropium bromide) Inhalation Aerosol.

We consider this a complete, class 2 response to our October 9, 2003, action letter. Therefore, the user fee goal date is November 17, 2004.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

If you have any question, call Ms. Ladan Jafari, Regulatory Project Manager, at (301) 827-1084.

Sincerely,

{See appended electronic signature page}

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

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/s/

Badrul Chowdhury
6/7/04 09:27:13 AM



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

FACSIMILE TRANSMITTAL SHEET

DATE: May 4, 2004

To: George Chen	From: Ladan Jafari
Company: BIPI	Division of Pulmonary and Allergy Drug Products
Fax number: 203-791-6262	Fax number: 301-827-1271
Phone number: 203-798-4942	Phone number: 301-827-1084
Subject: NDA 21-527	

Total no. of pages including cover: 5

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NDA 21-527

Drug: Atrovent HFA Inhalation Aerosol

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI)

Telecon Date: April 15, 2004

IMTS: 12631

BIPI Representatives:

Thomas Hampe, Ph.D., R&D Project Manager

Paul Jager, Pharmaceutical Sciences

George Chen, Ph.D., Technical Drug Regulatory Affairs

Dan Norwood, Ph.D., Analytical Sciences

Dennis O'Connor, Analytical Sciences

Terrence Tougas, Ph.D., CMC Expert

Gordon Hansen, Analytical Sciences

Pat Watson, Technical Drug Regulatory Affairs

Division of Pulmonary & Allergy Drug Products (DPADP) Representatives:

Prasad Peri, Ph.D., CMC Reviewer

Alan Schroeder, Ph.D., CMC Reviewer

Richard Lostritto, Ph.D., CMC Team Leader

Lori Garcia, R.Ph., Regulatory Project Manager

Ladan Jafari, Regulatory Project Manager

Background: BIPI submitted a meeting request dated February 20, 2004, to discuss some of the deficiencies of the Approvable letter dated October 9, 2003, for Atrovent HFA. BIPI also submitted a briefing package dated March 26, 2004, which contained a list of questions to be discussed at this meeting. Upon review of this briefing package, the Division sent a telephone facsimile dated April 7, 2004, indicating that the briefing package submitted by BIPI contains data that is normally submitted as part of a complete response to an approvable letter, and it appears that BIPI is seeking for agreements that require an in-depth review. The Division asked that BIPI rephrase their questions in order to achieve a more productive meeting. BIPI submitted a general correspondence dated April 12, 2004, which contained their rephrased questions for this meeting.

Dr. Lostritto initiated the meeting by acknowledging that he participated in the development of ipratropium bromide HFA inhalation aerosol when he worked at BIPI, and is aware of most issues with that drug product, and that the Division will approach all issues with a scientific point of view. Dr. Lostritto further explained that the Division's telephone facsimile of April 7, 2004, was to let BIPI know that we are amenable to any meetings to discuss scientific approaches to any outstanding issues of an application, however, we cannot agree or disagree on those approaches until we have fully reviewed a complete response to an application. The following questions of BIPI's April 12, 2004, correspondence were discussed.

NDA 21-527

Drug: Atrovent HFA Inhalation Aerosol

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI)

Telecon Date: April 15, 2004

IMTS: 12631

Page 2

Comment 11.(h)(2): This pertains to the stability results for samples stored at 40°C/85%RH.

BIPI proposed to provide stability results measured _____ for samples stored at 40°C/85%RH post approval. The Division agreed that this study could be done post-approval, however discussed the following issues with this study:

- **Number of batches to be studied:** BIPI proposed to do 3 validation batches. These validation batches are scheduled for production in the third quarter of 2004.
- **Conditions:** The Division is concerned that there is a trend between _____ for both orientations and for the means of all batches. BIPI indicated that they do not believe there is a downward trend, and indicated that the Division will agree with BIPI after the results of the three validation batches are reviewed. The Division stated that BIPI should submit their argument and support it statistically. The Division noted that we have seen a drastic drop at 40°C/85%RH condition but not at other storage conditions, however, if BIPI can provide data and support it statistically that there is no change in the aerodynamic particle size distribution (APSD), then that could be addressed as well in the full response and does not need to be done post-approval.
- **Time points:** The Division suggested that these batches be studied at _____ month time points in both upright and inverted orientations. BIPI indicated that they were planning to do _____ studies for only _____. The Division indicated that we believe a _____ time point will give a better understanding of the data, however, BIPI can propose a weekly analysis if they think that it is more appropriate. BIPI indicated that they will consider the Division's suggestions and will consider a _____ time point.
- **Data submission:** BIPI asked if they should submit these data on a _____ basis or they should send a package containing all cumulative data. The Division stated that we would like to see one package containing all data, however, if BIPI sees any remarkable changes in the interim, we advise that BIPI share that information with the Division. BIPI asked as to whether this data need to be submitted in the annual report or submitted as a general correspondence to the application. The Division asked that BIPI discuss this issue with the Division prior the submission. If there is any action needed for the information submitted, then a submission of a supplement is warranted.

NDA 21-527

Drug: Atrovent HFA Inhalation Aerosol

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI)

Telecon Date: April 15, 2004

IMTS: 12631

Page 3

Comment 11.(h)(3): This pertains to the profile of APSD.

BIPI had asked for clarification on three issues in this question. These issues are identified below:

- **Clarification of the Division's comment regarding significant change in APSD.**
This was discussed in detail under question 11.(h)(2).
- **Clarification of the term "fine particle fraction" with respect to the stages of the Anderson Cascade Impactor (CI):** The Division indicated that there is no universal agreement, but there are multiple working definitions of "fine particle fraction" used for approved products. Because Atrovent HFA is not a suspension, we would like to define "fine particle fraction" as including the mass on stages that capture particles μ in diameter and below.
- **Clarification of the Division's comment to [redacted] : BIPI**
proposed stage groupings [redacted]
[redacted] BIPI asked if this proposal was reasonable.

**APPEARS THIS WAY
ON ORIGINAL**

NDA 21-527

Drug: Atrovent HFA Inhalation Aerosol

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI)

Telecon Date: April 15, 2004

IMTS: 12631

Page 4

Comments 33(h) and 37(H): These questions pertain to control of and any potential _____ extractable in the drug product.

BIPI indicated that they have a validated method for _____ but not for _____. The Division clarified that _____ and _____ could come from _____.

_____ Therefore, there should be controls for both of these contaminant classes in the drug product. The Division stated that the request for control of _____ and _____ is required of all applicants, and we will not accept any proposal that would eliminate the control of any one of them. BIPI indicated that the original submission contains information regarding the control of _____ and the corresponding validated method. At this time BIPI do not have a validated method for _____ and asked if they could provide a method for _____ post-approval. The Division stated that BIPI should put a proposal for the Division's review and feedback. This proposal could be submitted as part of the complete response to the application.

Action: BIPI plans to submit a complete response to the Division's approvable letter of October 9, 2003, by end of April 2004. BIPI will include a proposal for control of _____ as part of the complete response. BIPI agreed that their complete response will be supported with a statistical analysis plan.

**APPEARS THIS WAY
ON ORIGINAL**

NDA 21-527

Drug: Atrovent HFA Inhalation Aerosol

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI)

Telecon Date: April 15, 2004

IMTS: 12631

Page 5

Drafted by: LJ/4-22-04

Initialed by: Peri/4-29-04
Schroeder/4-29-04
Lostritto/4-29-04

Filename: N21527Apr04tconmin.doc



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

FACSIMILE TRANSMITTAL SHEET

DATE: April 7, 2004

To: George Chen	From: Ladan Jafari
Company: BIPI	Division of Pulmonary and Allergy Drug Products
Fax number: 203-791-6262	Fax number: 301-827-1271
Phone number: 203-798-4942	Phone number: 301-827-1084
Subject: NDA 21-527	

Total no. of pages including cover: 3

Comments: CMC comments

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If _____ and/or _____ do appear at the _____ level, you will need to introduce contingency plans to commence _____ and/or _____ testing : _____ level as leachables for a period which assures that proper control has been reestablished.

Regarding comment 11.h(2), a preliminary assessment of the data provided in your amendment indicate that there is a consistent downward trend in the data at 40C/85%RH from _____, for both orientations which does not appear to be random. Your complete response to the approvable letter should address this result.

Regarding comment 13, your proposal that the requested stability study for foreign particulates ex-valve begin as a post-approval stability commitment is acceptable. However, the detailed particulars of the method and acceptance criteria are review issues that will be addressed during the assessment of your complete response to the approvable letter.

I may be reached at 301-827-1084 for any questions.

Ladan Jafari, Regulatory Project Manager

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/s/

Ladan Jafari
4/7/04 04:38:08 PM
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MEMORANDUM OF TELECON

DATE: March 23, 2004

APPLICATION NUMBER: NDA 21-527, Atrovent HFA (ipratropium bromide) (Inhalation Aerosol)

BETWEEN:

Name: Jeffrey Snyder, Senior Associate Director, Drug Regulatory Affairs
Phone: 203-778-7727
Representing: BIPI

AND

Name: Ladan Jafari, Regulatory Project Manager
Division of Pulmonary and Allergy Drug Products, HFD-570

SUBJECT: Dose actuation indicator development plans

Background: BIPI submitted a general correspondent dated March 5, 2004, which included an update on the status of BIPI's activities on the development of the dose actuation indicator program. BIPI proposed to address the dose actuation indicator as a Phase 4 commitment and plans to submit a prior approval supplement to incorporate the dose actuation indicator for NDA 21-527 approximately — after the Atrovent HFA NDA is approved.

I contacted BIPI to inform them that we do not have any objections to BIPI's proposed plan and schedule for development and implementation of the dose actuation indicator for Atrovent HFA.

Ladan Jafari
Regulatory Project Manager

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/s/

Ladan Jafari
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Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: January 8, 04

To: George Chen	From: Ladan Jafari
Company: BIPI	Division of Pulmonary and Allergy Drug Products
Fax number: 203-791-6262	Fax number: 301-827-1271
Phone number: 203-798-4942	Phone number: 301-827-1084
Subject: NDA 21-527	

Total no. of pages including cover: 6

Comments: CMC meeting minutes

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NDA 21-257
Drug: Atrovent HFA
Applicant: BIPI
Date of Telecon: December 19, 2003
IMTS: 11760

BIPI Representatives:

George Chen, Technical DRA
Terrance Tougas, Analytical Sciences
Dennis O'Connor, Analytical Sciences
Gordon Hansen, Analytical Sciences
Paul Jager, Pharmaceutics
Stephen Wolfrey, PKG Development

Division of Pulmonary & Allergy Drug Products (DPADP) Representatives:

Prasad Peri, CMC Reviewer
Alan Schroeder, CMC Reviewer
Ladan Jafari, Regulatory Project Manager

Background: BIPI submitted a request for either a teleconference or a meeting dated November 4, 2003, to discuss a few questions of the approvable letter issued on October 9, 2003 for Atrovent HFA. BIPI requested to discuss questions 10.b., 11.g., 12.g., 13., 14., 16., 17., 18., 21., 22., and 26. of the approvable letter. BIPI also submitted another document dated November 18, 2003, which contained a request for clarification for question 12. of the approvable letter. These questions are printed in Italics below followed by the Division's responses and any discussions that took place during this telecon.

10.b. : *Implement a validated analytical method (e.g., GC-MS) that corroborates the results of the COA for HFA-134a obtained from — Provide a description of the method and adequate method validation data.*

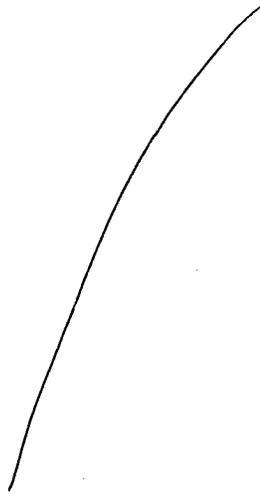
The Division agreed that the proposal to have 3M conduct the testing is acceptable as long as the following is provided: a Letter of Authorization from 3M, the method number, application number and product for which the method is approved, and verification that the test method performed by 3M is validated for its product(s). In addition the Division clarified that the proposed GC — method is sufficient and a second GC-MS method is not necessary.

11.g. : *The following comments pertain to the acceptance criterion for dose content uniformity. Based on the average unit dose content obtained for the primary stability and demonstration batches, revise the target medication delivery to 17 micrograms per actuation.*

NDA 21-257
Drug: Atrovent HFA
Applicant: BIPI
Date of Telecon: December 19, 2003
IMTS: 11760
Page 2

The Division clarified that 17 micrograms per actuation is considered the same as 17 micrograms when rounded off to two significant figures, and stated that if the target actuation delivers 17 micrograms of the drug, it can be labeled as 17 micrograms. It was noted that two significant figures are used for labeling the Atrovent CFC product. No changes to the specifications are needed.

12.g. : *The following comments pertain to the determination of medication delivery: BIPI TP-00471-05 method for content uniformity and unit spray content. (2) Modify and combine these methods such that 10 canisters are tested at beginning of can life and the same 10 canisters are tested for the end of the can life.*

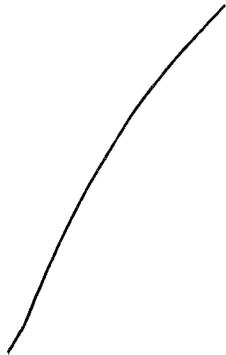


13. : *Provide data for foreign particulates as a function of time, to enable evaluation of any trends in the data over time and of the reliability of the analytical method.*

BIPI clarified that the data they had submitted previously were for 10 time point and that they had inadvertently identified the data as 10 time point. They only have single point data which the Division found to be inadequate. BIPI indicated that they don't have any new product right now for new stability studies. BIPI asked if they could provide a post-approval commitment for this issue. The Division indicated that such a commitment may be acceptable, but we'd need to discuss it internally. The Division would like to see a specification for foreign particulates in the emitted dose.

NDA 21-257
Drug: Atrovent HFA
Applicant: BIPI
Date of Telecon: December 19, 2003
IMTS: 11760
Page 3

The Division asked that BIPI address the reliability of the counting method. —



The Division also clarified that the foreign particulates are a concern since the patients will be exposed to them chronically.

14. : *The following comments pertain to the studies involved in the characterization of impurities described in the report U02-3347 (vol. 7, pages 199-234). Add acceptance criteria for — since they appear above the limit of quantitation consistently over time during the stability studies as indicated on page 206, vol. 7.*

The Division clarified that an acceptance criterion needs to be added for the —

16. : *In the experiments described under the "Effect of Resting Time in vol. 3 page 156" provide the results of the testing time on individual actuation basis and not based on a dose (2 actuations). Comments on the conditions needed to re-prime the canister are being withheld until data on the individual actuations are provided.*

BIPI indicated that they believe they have provided sufficient information to establish that two actuations are needed to prime the aerosol valve initially or to re-prime the valve after periods of non-use exceeding 72 hours. The Division agreed with BIPI's proposal based on our re-review of the previously submitted data.

17. : *Based on the results of the priming studies modify the patient instructions as follows. "Patients should "Prime" or actuate the drug product — times prior to taking the first dose from a new inhaler".*

As with question 16 above, the Division agrees with BIPI's proposal.

18. : *In the experiments performed under the topic "cleaning instructions" provide data to justify that weekly cleaning of the actuator is optimal in terms of content uniformity and APSD.*

The Division clarified that we wanted to know if BIPI had any justification for choosing 7 days for cleaning or if 7 was an arbitrary number. BIPI indicated that they based this decision on their previous experience with studies with solutions as well as comparing their label with competitor's products labeling. BIPI indicated that they did not perform a specific study to assess the optimum number of days for a cleaning interval. The Division asked BIPI to provide Aerodynamic Particle Size Distribution (APSD) data for the drug product before and after undergoing the cleaning procedure (e.g. in a patient-use simulation) and after 30 days without cleaning. The Division also asked if BIPI had any results for APSD or dose content uniformity or shot weight for canisters that were actuated using the mouthpiece without cleaning procedure. BIPI indicated that they did not have such data. BIPI asked if they could provide the APSD data on another lot. The Division responded that BIPI could provide APSD data on a representative commercial lot.

21. : *Provide available individual ACI results rather than pooled data including an evaluation of the APSD and mass balance data from studies on _____ for products manufactured from the second and third generation container closure systems.*

BIPI indicated that they have individual results and will provide those data.

22. : *Provide available APSD data comparing the methods _____ for drug product stored at the same time points during stability.*

The Division indicated that based upon BIPI's clarification, no additional information is needed at this time.

26. : *Drawings with labeled dimensions are only provided for the stem receptacle and spray orifice of the mouthpiece, and legibility of the number is poor (vol. 13, page 32). Provide legible drawings of the entire mouthpiece component labeled with precise dimensions.*

The Division clarified as was indicated earlier, that we need to see labeling for the mouthpiece. BIPI asked if the Division would consider any other labeling approaches besides _____

NDA 21-257

Drug: Atrovent HFA

Applicant: BIPI

Date of Telecon: December 19, 2003

IMTS: 11760

Page 5

12.g. : *The following comments pertain to the determination of medication delivery: BIPI TP-00471-05 method for content uniformity and unit spray content. (1) Delete the phrase that states that*

where this is stated.

This comment also applies to other methods

BIPI clarified that

With this clarification, the Division indicated that the above mentioned phrase does not need to be deleted from the methods.

Actions: BIPI plans to submit the response to this application in April 2004. BIPI asked if the Division would consider "the particle characterization and the trend" a major deficiency. BIPI asked if the characterization study could be done post approval. The Division stated that BIPI could submit any justification for post approval studies in their response to the application, and we would discuss this internally.

**APPEARS THIS WAY
ON ORIGINAL**

NDA 21-257
Drug: Atrovent HFA
Applicant: BIPI
Date of Telecon: December 19, 2003
IMTS: 11760
Page 6

Drafted by: LJ/12-23-03

Initialed by: Peri/1-7-04
Schroeder/1-7-04
Bertha/1-8-04

Filename: N21527Dec03Tconmin.doc

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/s/

Ladan Jafari
1/8/04 03:26:55 PM

IND 45,938

MEMORANDUM OF MEETING MINUTES

MEETING DATE: May 26, 2000
TIME: 1:00 P.M.
LOCATION: Potomac Conference Room
APPLICATION: IND 45,938 (ipratropium bromide inhalation aerosol)
TYPE OF MEETING: Face to Face

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

<u>Name of FDA Attendee</u>	<u>Title</u>	<u>Division Name & HFD#</u>
1. Raymond Anthracite	Clinical Reviewer	HFD-570 DPADP
2. Craig Bertha	Chemistry Reviewer	HFD-570 DPADP
3. Young-Moon Choi	Clinical Pharmacology & Biopharmaceutics Reviewer	HFD-570 DPADP
4. Badrul Chowdhury	Clinical Team Leader	HFD-570 DPADP
5. James Gebert	Biometrics Reviewer	HFD-570 DPADP
6. Ladan Jafari	Project Manager	HFD-570 DPADP
7. Robert Meyer	Division Director	HFD-570 DPADP
8. Guirag Poochikian	Chemistry Team Leader	HFD-570 DPADP
9. Alan Schroeder	Chemistry Reviewer	HFD-570 DPADP
10. Peter Starke	Clinical Reviewer	HFD-570 DPADP
11. Ramana Upoor	Clinical Pharmacology & Biopharmaceutics Team Leader	HFD-570 DPADP

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

<u>External Attendee</u>	<u>Title</u>	<u>Sponsor/Firm Name</u>
1. Nora Fagan	Statistics	BIPI
2. David Falconer	Research & Development Project Management	BIPI
3. Arne Froemder	International Project Management	BIPI
4. Mo Ghafouri	Clinical Research	BIPI
5. Thomas Hampe	Research & Development Project Management	BIPI
6. Paul Jager	Pharmaceutics	BIPI
7. Marty Kaplan	Vice president Regulatory Affairs	BIPI
8. Tom MacGregor	Drug Metabolism & PK	BIPI
9. Alan McEmber	Regulatory Affairs	BIPI
10. Shailendra Menjoge	Associate Director, Statistics	BIPI
11. Ted Witek	Head, Clinical Research	BIPI

BACKGROUND: BIPI submitted a request for a meeting to discuss the modifications made to the product during and after the course of the clinical development. BIPI requested this meeting to discuss the existing CMC and clinical program in support of a NDA filing. A briefing package was submitted to the Division Dated March 22, 2000, (attachment 1.)

Summary:

Question 1.1 of the briefing package, which pertains to changes in the valve after the conduct of the clinical program: The Division noted that since the performance data utilizing the 3rd generation valve for only one batch of the drug product was submitted, the Division could not respond to that question without reviewing additional comparative data that should include the following.

1. Spray pattern, plume geometry, extractables/leachables profile (including for example, organic, talc, and metal ion leachables), foreign particulates, and full performance data (including multiple representative batches of the drug product with multiple batches of the 3rd generation valve.)
2. Extractables/leachables and foreign particulates should be compared on stability. If the profile of extractables/leachables has changed, it may raise qualification issues.

BIPI stated that they would generate additional data to fully understand the profile of the extractables, however, they asked why we were concerned about — The Division raised concerns about the potential presence of —

— BIPI indicated that they would provide additional data as requested.

Question 1.2 of the briefing package, which pertains to a proposed adjustment of the medication delivery target: The Division stated that it was premature to respond to that question, considering the amount of information submitted for the third generation valve. The mean valve deliveries reported (page 42) appear to be somewhat lower for products containing the third generation valve compared to first and second generation valves. Paradoxically, the data for medication delivery (pages 43 and 44) are somewhat higher for products containing the third generation valve compared to the first and, second generation valves. The Division stated that there should be direct relationship between the valve delivery data and medication delivery data for solutions and therefore, this discrepancy should be scientifically explained and justified. The Division further specified that the adjustment in medication delivery target may be satisfactory, if it accurately reflects the data obtained for the drug product incorporating each individual valve generation. BIPI stated that they plan to do further studies with the third generation valve and will provide additional data for review.

The Division cautioned BIPI that there should not be any major differences between the device used in the clinical batches and the to-be-marketed device. The performance of the drug product should be shown to be comparable across changes in the manufacturing site and manufacturing process (e.g.,

The Division also stated that the majority (by mass) of the drug product which collects on the cascade impactor stages is of the finer particle size (and below.) Data provided on page 29 show that more drug is in this finer particle size fraction for the drug product containing the first generation valve compared to the third generation valve. These differences may raise some concerns. Also paradoxically, the amount of drug that collects on the is greater for the drug product manufactured with the third generation valve, compared to the drug product manufactured with the first generation valve. The reason for this discrepancy should be clarified. BIPI also stated that for the NDA batches, they plan to use and are using the USP method. The Division stated that the effect of upon the particle size distribution results should be adequately demonstrated with appropriate data. BIPI stated that they intend to submit data to compare the

The Division stated that the proposed acceptance criterion for individual values of valve delivery (\pm) is too broad and not acceptable.

Question 2 of the briefing package: The Division stated that since the first and second generation valves are no longer available, there will not be a way to do bridging studies between the different valves. Therefore, in the absence of any new extractables/leachables in the drug substance, one single dose, dose-ranging, cross-over study using CFC and the to-be-marketed HFA product is sufficient for review. The Division emphasized that if there are any new peaks in the chromatogram of the extractable profile in the third generation valve, BIPI will need to characterize the new peaks based on further studies. The Division also stated that they are not looking for a bioequivalence study and recommended trial designs such as looking at the 42 and 84 μg dose, and 1 puff and 2 puffs vs. placebo. BIPI agreed to the Division's comments. The Division reminded BIPI that the recommendation of one single dose study was only acceptable in this particular case, since we are dealing with an inhalation solution product, and given the changes proposed.

With regard to the 7-day pharmacokinetic trial in COPD patients, the Division stated that bioequivalence based on PK alone is not sufficient. To characterize comparative bioavailability between CFC and HFA formulations, BIPI should obtain pharmacokinetic information after single dose and at the steady state after multiple-dose. Specifically, BIPI should obtain single dose pharmacokinetic information (i.e., obtain urine samples for 24 hours and, plasma concentrations for adequate time) before starting the multiple dose phase for 7 days (dosing to steady state), and should ensure that the steady state is achieved by comparing three trough concentrations. The dose for pharmacokinetic study should be the highest recommended dose, and if low concentrations are expected, a dose higher than recommended may be added to this study. The Division also indicated that the proposals for the wash-out period, cross-over design, number of subjects and blood sampling are acceptable as proposed. The Division stated that the pharmacokinetic study should preferably be done as a separate study and not as a subset of the clinical trial.

BIPI asked for more clarification regarding the requirement of the pharmacokinetic study at the highest recommended dose. The Division stated that BIPI definitely needs to provide information at the highest recommended dose, since the current studies do not detect anything after single low doses. BIPI also indicated that the half life of ipratropium bromide is not more than 1.5 hours, and there are no plasma levels beyond 2 hours even in the 84 µg dose, they would not observe any accumulation at day 7. Therefore, the trough concentrations may not be observed. The Division requested that BIPI provide the justification and protocols for review before they initiate the studies. BIPI agreed to do as recommended.

Other general issues: The Division inquired about the reasons for changing of the valve in this IND, and BIPI responded that the change from generation 1 valve to generation 2 was to reduce the amount of extractables due to the —————. They went from generation 2 to generation 3 valves to improve the mechanical strength of the valve seals and the robustness of the product.

Post-meeting notes: In a discussion with Dr. Schroeder after the meeting, BIPI stated that they do not have plume geometry or — data on the first and second generation valve products. Dr. Schroeder responded that — may be a patient safety issue and data on the to-be-marketed product is probably most important. The Division can not give an okay right now in advance of the NDA. BIPI should provide all data that they can obtain and we will assess whether it is sufficient to support the valve changes.

IND 45,938
Page 6

cc: Original IND 45938
HFD-570/Div. Files
HFD-570/Jafari
HFD-570/Anthracite
HFD-570/Chowdhury
HFD-570/Choi
HFD-570/Uppoor
HFD-570/Gebert
HFD-570/Schroeder
HFD-570/Poochikian

Drafted by: LJ/6-7-00

Initialed by: Anthracite/6-8-00
Chowdhury/6-9-00
Choi/6-9-00
Uppoor/6-16-00
Schroeder/6-12-00
Poochikian/6-13-00

FILENAME: I45938MINUTES

MEETING MINUTES



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

FACSIMILE TRANSMITTAL SHEET

DATE: July 18, 2003

To: George Chen	From: Ladan Jafari
Company: BIPi	Division of Pulmonary and Allergy Drug Products
Fax number: 203-791-6262	Fax number: 301-827-1271
Phone number: 203-7978-4942	Phone number: 301-827-1084

Subject: NDA 21-527

Total no. of pages including cover: 5

Comments: Meeting minutes

Document to be mailed: YES NO

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NDA 21-527
Drug: Atrovent HFA
Applicant: BIPI
Teleconference Date: July 9, 2003
IMTS: 11028

BIPI Representatives:

George Chen, Technical Drug Regulatory Affairs, BI
Mohamed Ghafouri, Clinical Research, BI
Eben Rubin, Clinical Research, BI
Terrence Tougas, Analytical Sciences, BI
Paul Jager, Pharmaceutical Sciences, BI
David Kennedy, Director, Dose Counting Program, Trudell Medical International (TMI)
Thomas Hampe, R&D Project Management, BI

Division of Pulmonary & Allergy Drug Products (DPADP) Representatives:

Prasad Peri, Ph.D., CMC Reviewer
Alan Schroeder, Ph.D., CMC Reviewer
Brian Rogers, Ph.D., CMC Reviewer
Guirag Poochikian, Ph.D., CMC Team Leader
Marianne Mann, M.D., Deputy Director
Tejashri Purohit-Sheth, M.D., clinical Reviewer
Lydia Gilbert-McClain, M.D., Acting Medical Team Leader
Badrul Chowdhury, M.D., Ph.D., Director
Ladan Jafari, Regulatory Project Manager

BIPI submitted a request for a meeting on June 6, 2003, to discuss the development plans for the dose counter for Atrovent HFA. A separate meeting was held with BIPI on April 28, 2003, regarding this issue. BIPI requested this teleconference to further discuss the proposal for . —

3 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

 § 552(b)(4) Draft Labeling

NDA 21-527

Drug: Atrovent HFA

Applicant: BIPI

Teleconference Date: July 9, 2003

IMTS: 11028

Page 5

Drafted by: LJ/7-11-09

Initialed by: Rogers/7-16-03

Schroeder/7-16-03

Peri/7-16-03

Poochikian/7-16-03

Purohit-Sheth/7-14-03

Mann/7-11-03

Chowdhury/7-16-03

Filename: Atrovent HFA dose counter.doc



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

FACSIMILE TRANSMITTAL SHEET

DATE: June 19, 2003

To: Jeffrey Snyder	From: Ladan Jafari
Company: BIPI	Division of Pulmonary and Allergy Drug Products
Fax number: 203-778-7357	Fax number: 301-827-1271
Phone number: 203-778-7727	Phone number: 301-827-1084
Subject: NDA 21-527	

Total no. of pages including cover: 2

Comments:

Document to be mailed: YES NO

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NDA 21-527

Dear Mr. Snyder:

We are reviewing your NDA for Atrovent HFA and have the following requests for information.

1. Provide Appendix 15.12, listing 1: a full listing of patient disposition by center.
2. Provide a summary of the protocol violations by treatment group and number of patients with each protocol violation per treatment group.
3. You have referenced Appendix 15.12, listing 2; however, we are unable to locate this in this study's volumes. Please provide this Appendix.
4. You have listed the mean weight range for subjects as 30-123 kg. How many subjects in the study weighed under a 100 lbs(45 kg) and what were their respective weights?
5. Provide a summary of concomitant therapy and concomitant diseases of the subjects enrolled in this study.
6. Ipratropium bromide pharmacokinetic results delivered from the CFC formulation were not consistent across studies. The AUC values (dose normalized) were much lower (4-fold) in study U95-0343 compared to study U01-3343. Provide an explanation for these unexpected results and submit cross-study validation data comparing bioanalytical assays.

If you have any questions, I may be reached at 301-827-1084.

Ladan Jafari, Regulatory Project Manager

NDA 21-527

Page 2

Initialed by: Barnes/6-18-03
Purohit-Sheth/6-18-03
Gilbert-McClain/6-18-03
Suarez/6-18-03
Fadiran/6-18-03

Filename:N21527Clinquestions.doc

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/s/

Ladan Jafari
6/19/03 09:10:08 AM
CSO



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

FACSIMILE TRANSMITTAL SHEET

DATE: July 14, 2003

To: George Chen	From: Ladan Jafari
Company: BIPI	Division of Pulmonary and Allergy Drug Products
Fax number: 203-791-6262	Fax number: 301-827-1271
Phone number: 203-7978-4942	Phone number: 301-827-1084
Subject: NDA 21-527	

Total no. of pages including cover: 2

Comments:

Document to be mailed: YES NO

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NDA 21-527

The following comments pertain to NDA 21-527, amendment dated June 12, 2003. They are in response to your request for clarification of our information request letter dated May 6, 2003.

This pertains to comment 3. The mouthpiece should contain the following — labeling:

Please disregard comment 9c. It was intended to apply to valve components. This is addressed in comment 14c.

This pertains to comment 15a. The phrase “improve the capability” of the spray pattern method refers to developing a method that can distinguish unacceptable mouthpieces from acceptable mouthpieces.

If you have any questions, I may be reached at 301-827-1084.

Ladan Jafari, Regulatory Project Manager

NDA 21-527
Page2

Initialed by: Barnes/7-9-03
Schroeder/7-11-03
Poochikian/7-11-03

Filename: N21527CMCcomments7-9-03

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/s/

Ladan Jafari
7/14/03 08:53:01 AM
CSO

IMS
10465

Memorandum of Telephone Facsimile Correspondence

Date: June 10, 2003

To: George T. Chen, Ph.D.
Senior Associate Director, Technical Drug Regulatory Affairs

Fax: 203-791-6262

From: Christine Yu, R.Ph.
Regulatory Project Manager

Subject: NDA 21-527 Atrovent HFA-134a (ipratropium bromide) Inhalation aerosol
Minutes of April 28, 2003, teleconference

Reference is made to the meeting/teleconference held between representatives of your company and this Division on April 28, 2003. Attached is a copy of our final minutes for that meeting/teleconference. These minutes will serve as the official record of the meeting/teleconference. If you have any questions or comments regarding the minutes, please call me at (301) 827-1051.

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Thank you.

E

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§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

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/s/

Christine Yu
6/10/03 11:00:40 AM



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

FACSIMILE TRANSMITTAL SHEET

DATE: May 6, 2003

To: George Chen	From: Ladan Jafari
Company: BIPI	Division of Pulmonary and Allergy Drug Products
Fax number: 203-791-6262	Fax number: 301-827-1271
Phone number: 203-798-4942	Phone number: 301-827-1084

Subject: Atrovent HFA

Total no. of pages including cover: 8

Comments:

Document to be mailed: YES NO

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F

7 Page(s) Withheld

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§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

NDA REGULATORY FILING REVIEW
(Includes Filing Meeting Minutes)

NDA Number, Requested Trade Name, Generic Name and Strengths (modify as needed for an efficacy supplement and include type): NDA 21-527 Atrovent HFA (ipratropium bromide) Inhalation Aerosol

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

Date of Application: December 6, 2002

Date of Receipt: December 9, 2002

Date of Filing Meeting: February 3, 2002

Filing Date: February 7, 2002

Indication(s) requested: _____, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

Type of Application: Full NDA Supplement _____

(b)(1) (b)(2) _____

[If the Original NDA of the supplement was a (b)(2), all subsequent supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or (b)(2)]

If you believe the application is a 505(b)(2) application, see the 505(b)(2) requirements at the end of this summary.

Therapeutic Classification: S S P _____

Resubmission after a withdrawal or refuse to file N _____

Chemical Classification: (1,2,3 etc.) 3 _____

Other (orphan, OTC, etc.) None _____

Has orphan drug exclusivity been granted to another drug for the same indication -----YES----- NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES NO

If the application is affected by the application integrity policy (AIP), explain.

User Fee Status: Paid _____ Waived (e.g., small business, public health) _____

Exempt (orphan, government) _____

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

User Fee ID# 4445

Clinical data? YES NO _____ Referenced to NDA# _____

Date clock started after UN N/A _____

User Fee Goal date: October 9, 2003

Action Goal Date (optional) September 25, 2003

• Does the submission contain an accurate comprehensive index? ---X YES NO

• Form 356h included with authorized signature? ---X YES NO

If foreign applicant, the U.S. Agent must countersign.

- Submission complete as required under 21 CFR 314.50? --X YES --NO
 If no, explain:
- If electronic NDA, does it follow the Guidance? ---YES ---NO X--- NA
If an electronic NDA: all certifications must be in paper and require a signature.
- If Common Technical Document, does it follow the guidance? --- YES ---NO X --NA
- Patent information included with authorized signature? --X YES -- NO
- Exclusivity requested? X If yes, _____ years X NO

Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.

- Correctly worded Debarment Certification included with authorized signature? X YES NO
If foreign applicant, the U.S. Agent must countersign.

Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as, "To the best of my knowledge,"

- Financial Disclosure included with authorized signature? --X YES NO
 (Forms 3454 and/or 3455)
If foreign applicant, the U.S. Agent must countersign.
- Has the applicant complied with the Pediatric Rule for all ages and indications? --X YES NO
 If no, for what ages and/or indications was a waiver and/or deferral requested: not applicable to the younger age group.
- Field Copy Certification (that it is a true copy of the CMC technical section)? ----X YES ---- NO

Refer to 21 CFR 314.101(d) for Filing Requirements

PDUFA and Action Goal dates correct in COMIS? ----X YES ---- NO
 If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

List referenced IND numbers: 45,938

End-of-Phase 2 Meeting? Date _____ X NO
 If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? X Date(s) March 27, 02 and January 16,
 02 _____ NO
 If yes, distribute minutes before filing meeting.

Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

If filed, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): Information that is submitted under section 505(b) or (c) of the act and 21 CFR 314.53 is for a method of use patent, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent.
- 21 CFR 314.54(a)(1)(iv): The applicant is seeking approval only for a new indication and not for the indication(s) approved for the listed drug(s) on which the applicant relies.

Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?
YES NO
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?
YES NO
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?
YES NO

Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: 2-6-03

BACKGROUND: Atrovent Inhalation Aerosol is an already approved drug for the treatment of COPD. The applicant is proposing this new formulation containing the HFA propellant since the CFC formulation of this product is being phased out due to its harmful effect on the environment.

ATTENDEES: Tejashri Purohit-Sheth, Lydia Gilbert-McClain, Marianne Mann, Alan Schroeder, Prasad Peri, Guirag Poochikian, Virgil Whitehurst, Sandra Suarez, Emmanuel Fadiran, James Gebert, Akila Green, Ladan Jafari

ASSIGNED REVIEWERS:

Discipline

Reviewer

Medical: Tejashri Purohit-Sheth
Secondary Medical: Lydia Gilbert-McClain
Statistical: James Gebert
Pharmacology: Virgil Whitehurst
Statistical Pharmacology: N/A
Chemist: Prasad Peri, Alan Schroeder
Environmental Assessment (if needed): Categorical exclusion requested.
Biopharmaceutical: Sandra Suarez
Microbiology, sterility: N/A
Microbiology, clinical (for antimicrobial products only): N/A
DSI: None needed
Project Manager: Ladan Jafari
Other Consults: None at this time.

Per reviewers, all parts in English, or English translation? ~~---~~X--YES _____ NO _____

CLINICAL – File X Refuse to file _____

• Clinical site inspection needed: YES _____ NO X

MICROBIOLOGY CLINICAL – File N/A Refuse to file _____

STATISTICAL – File X Refuse to file _____

BIOPHARMACEUTICS – File X Refuse to file _____

• Biopharm. inspection Needed: YES _____ NO X

PHARMACOLOGY – File X Refuse to file _____

CHEMISTRY – file

• Establishment(s) ready for inspection? YES X NO _____ File _____ Refuse to file _____

REGULATORY CONCLUSIONS/DEFICIENCIES:

 X The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

 The application is unsuitable for filing. Explain why:

 Ladan Jafari
Regulatory Project Manager, HFD-

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/s/

Ladan Jafari
5/2/03 02:33:59 PM
CSO



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

FACSIMILE TRANSMITTAL SHEET

DATE: March 24, 2003

To: Jeffrey Snyder	From: Ladan Jafari
Company: BIPI	Division of Pulmonary and Allergy Drug Products
Fax number: 203-778-7357	Fax number: 301-827-1271
Phone number: 203-778-7727	Phone number: 301-827-1084
Subject: Atrovent HFA	

Total no. of pages including cover: 2

Comments:

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-1050. Thank you.

NDA 21-527

Dear Mr. Snyder:

We are reviewing your NDA for Atrovent HFA and have the following requests for information.

1. Provide individual cumulative renal excretion data (amount in the 0-24hr collection period) following inhalation of ipratropium bromide-CFC given at a dose of 40 mcg and ipratropium bromide-HFA given at a dose of 40 and 80 mcg from study U96-0020.
2. Provide individual cumulative renal excretion data (amount in the 0-24hr collection period) following multiple inhalation of ipratropium bromide-CFC given at a dose of 40 mcg and ipratropium bromide-HFA given at a dose of 80 mcg from study U95-0343.
3. Provide individual PK parameters including the age of subjects enrolled in study U01-3343 in a tabulated form

If you have any questions, please contact me at 301-827-1084.

Ladan Jafari, Regulatory Project Manager

NDA 21-527

Page 2

Drafted by: LJ/3-19-03

Initialed by: Barnes/3-20-03

Suarez/3-20-03

Fadiran/3-20-03

Filename: N21527biopharmcomments.doc

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/s/

Ladan Jafari
3/24/03 09:30:23 AM
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: March 4, 2003

To: George Chen	From: Ladan Jafari
Company: BIPI	Division of Pulmonary and Allergy Drug Products
Fax number: 203-791-6262	Fax number: 301-827-1271
Phone number: 203-798-4942	Phone number: 301-827-1084
Subject: Atrovent HFA Inhalation Aerosol	
Total no. of pages including cover: 2	

Comments:

Document to be mailed: YES NO

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

1 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

NDA 21-527

Page 2

Initialed by: Barnes/3-3-03
Schroeder/3-4-03
Poochikian/3-4-03

Filename: N21527cmcinforequest.doc

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/s/

Ladan Jafari
3/4/03 01:20:43 PM
CSO



FILING REVIEW ISSUES IDENTIFIED

NDA 21-527

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P. O. Box 368
Ridgefield, CT 06877-0368

Attention: Jeffrey R. Snyder
Associate Director, Drug Regulatory Affairs

Dear Mr. Snyder:

Please refer to your December 6, 2002, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Atrovent HFA (ipratropium bromide HFA) Inhalation Aerosol.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on February 7, 2003, in accordance with 21 CFR 314.101(a).

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

The first generation Atrovent HFA product used in pivotal phase 3 clinical trials was subsequently changed to a second and then a third generation product intended for marketing. Significant changes in the overall drug product were made, with significant changes in particle size distribution noted. The chemistry, pharmacokinetic, and clinical reviewers will focus on the data that address these differences to see if there is adequate information to support approval of the third generation Atrovent HFA product.

We are providing the above comment to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We do not expect a response to the above comment, and we may not review any such response during the current review cycle.

We request that you submit the following information.

1. Provide a subset analysis of the safety and FEV₁ data for the patients who received the 1st and 2nd generation of the drug product in the one-year safety study 244.2453.
2. Provide a pharmacokinetic link between the to-be-marketed formulation and the formulations used in the pharmacokinetic and clinical trials.
3. Table 9.3.1:1 on page 56 in the study report of Study 244.1408 has 5 patients not included in the results a week after randomization. This same table on page 57 in the same study report has 4 patients not included in the last week. The data set DIARY (in the ISE \244.1408 Folder), however, has data values for all 172 patients at Week 1 and Week 12 (last week). Indicate which patients were excluded from these ITT analyses and why there are data values in the data set for these excluded patients.

Table 9.3.1.2:2 on page 65 of this study report has 12 patients not included in Visit 4 (day 42) and an unknown number not included at Visit 6 (day 84) {Most probably the numbers are 9 and 22 as in Table 9.3.1.2:1}. The data set PFT in ISE\244.1408 Folder has values for 172 patients. Indicate which patients were excluded from these ITT analyses and why there are data values in the data set for these excluded patients.

4. 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.
5. 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.
6. Provide ACI results including an evaluation of the APSD and mass balance data from studies on _____ for products manufactured from the first and third generation container closure system.
7. Design appropriate experiments to evaluate the APSD including particles _____ in size, i.e., the particles that are not captured by the _____. Provide such data for the first, second and third generation drug products. In addition, provide mass balance data for each of the above experiments.

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

NDA 21-527
Page 3

If you have any questions, call Ms. Ladan Jafari, Regulatory Project Manager, at (301) 827-1084.

Sincerely,

{See appended electronic signature page}

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

**This is a representation of an electronic record that was signed electronically and
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/s/

Badrul Chowdhury
2/21/03 08:15:17 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-527

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P. O. Box 368
Ridgefield, CT 06877-0368

Attention: Jeffrey R. Snyder
Associated Director, Drug Regulatory Affairs

Dear Mr. Snyder:

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

Name of Drug Product: Atrovent HFA (ipratropium bromide) Inhalation Aerosol

Review Priority Classification: Standard (S)

Date of Application: December 6, 2002

Date of Receipt: December 9, 2002

Our Reference Number: NDA 21-527

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 7, 2003, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 9, 2003.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:

Center for Drug Evaluation and Research
Division of Pulmonary & Allergy Drug Products
Attention: Division Document Room, Room 8b-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Ms. Ladan Jafari, Regulatory Project Manager, at (301) 827-1084.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Chief, Project Management Staff
Division of Pulmonary & Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Ladan Jafari
12/19/02 08:55:18 AM
Signed for Sandy Barnes.

USER FEE VALIDATION SHEET

NDA # 21-527 Supp. Type & # N-000 UFID # 4445
(e.g., N000, SLR001, SE1001, etc.)

1. YES NO User Fee Cover Sheet Validated? MIS_Elements Screen Change(s):

2. YES NO APPLICATION CONTAINS CLINICAL DATA?
(Circle YES if NDA contains study or literature reports of what are explicitly or implicitly represented by the application to be adequate and well-controlled trials. Clinical data do not include data used to modify the labeling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling).

REF IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE CROSS REFERENCED IN ANOTHER SUBMISSION.

3. YES NO SMALL BUSINESS EXEMPTION

4. YES NO WAIVER GRANTED

5. YES NO NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (other than bundling).
If YES, list all NDA #s, review division(s) and those for which an application fee applies.

NDA #	Division	Fee	No Fee
N _____	HFD- _____		
N _____	HFD- _____	Fee	No Fee

6. YES NO BUNDLING POLICY APPLIED CORRECTLY? No Data Entry Required
(Circle YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Circle NO if application should be split into more than one application or be submitted as an original instead of a supplement. If NO, list resulting NDA #s and review division(s).

NDA #	Division	NDA #	Division	RIA #
N _____	HFD- _____	N _____	HFD- _____	N _____

7. P S PRIORITY or STANDARD APPLICATION?

[Signature]
PM Signature / Date

[Signature] 12/2/02
CPMS Concurrence Signature / Date

2/14/00

2/14/00

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

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

1. APPLICANT'S NAME AND ADDRESS

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
Ridgefield, CT 06877

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
N021527

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

YES NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

(APPLICATION NO. CONTAINING THE DATA).

2. TELEPHONE NUMBER (Include Area Code)

(203) 778-7727

3. PRODUCT NAME

ATROVENT HFA (ipratropium bromide) Inhalation
Aerosol

6. USER FEE I.D. NUMBER

4445

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

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)

THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)

THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES NO

(See item 8, reverse side if answered YES)

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

Department of Health and Human Services
Food and Drug Administration
CDER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
and 12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

Jeff Snyder

TITLE

Associate Director, Drug Regulatory
Affairs

DATE

Vol 1 October 29, 2006

**CERTIFICATION: FINANCIAL INTERESTS AND
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

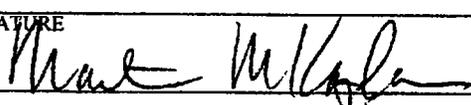
Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See attached list	
	<i>"An open-label, crossover, pharmacokinetic trial to determine the comparability of ipratropium bromide HFA-134a inhalation aerosol to the market standard, ATROVENT® CFC Inhalation Aerosol in patients with Chronic Obstructive Pulmonary Disease (COPD)" trial 244.2480</i>	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Martin M. Kaplan, M.D, J.D.	TITLE Vice President Drug Regulatory Affairs
FIRM/ORGANIZATION Boehringer Ingelheim Pharmaceuticals, Inc.	
SIGNATURE 	DATE 22 May 2002

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

**CERTIFICATION: FINANCIAL INTERESTS AND
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

TO BE COMPLETED BY APPLICANT

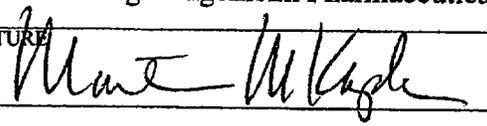
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See attached list	
	"A Single-Dose, Double-Blind, Crossover Trial to Determine the Comparability of Ipratropium Bromide HFA-134a Inhalation Aerosol to the Market Standard, ATROVENT® CFC Inhalation Aerosol, in Patients with Chronic Obstructive Pulmonary Disease (COPD)" trial 244.2498	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	Martin M. Kaplan, M.D, J.D.	TITLE	Vice President Drug Regulatory Affairs
FIRM/ORGANIZATION	Boehringer Ingelheim Pharmaceuticals, Inc.		
SIGNATURE		DATE	22 May 2002

Paperwork Reduction Act Statement

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Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

19.0 FINANCIAL INFORMATION

Certification: Financial Interests and Arrangements of Clinical Investigators

Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI), is a subsidiary of Boehringer Ingelheim GmbH (BIGmbH), a privately-held German company. As a privately-held company, BIGmbH is not publicly traded on any stock exchange, has no equity available to investigators and does not, as a matter of policy, provide compensation to investigators based on the outcome of studies conducted on its behalf. In addition, no investigators can have or own a proprietary interest in a product, trademark, licensing agreement or patent owned by the company.

Of the clinical trials that could be covered by the Financial Disclosure Rule, as described in 21 CFR 54, only the US open-label pharmacokinetic trial (244.2480) and Dose-confirmation trial (244.2498) were either on-going or conducted as of February 2, 1999. All other trials covered by the regulation¹ described in 21 CFR 54 were completed prior to February 2, 1999.

At this time we can certify that no investigators conducting COPD efficacy studies or Dose-confirmation studies conducted/completed prior to February 2, 1999 in support of the ipratropium bromide HFA NDA had any disclosable financial arrangements with Boehringer Ingelheim Pharmaceuticals, its parent company or subsidiaries.

Certifications (FDA Form 3454) and investigator/sub-investigator information are attached for the Pk (244.2480) and dose-confirmation (244.2498) studies.

¹ COPD Efficacy Studies:
244.1405
244.1408
244.2453
Dose-Confirmation Studies:
244.1403
244.1404

H

6 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling



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

FACSIMILE TRANSMITTAL SHEET

DATE: May 1, 2002

To: Mr. Jeff Snyder	From: Ladan Jafari
Company: BIPI	Division of Pulmonary and Allergy Drug Products
Fax number: 203-778-7357	Fax number: 301-827-1271
Phone number: 203-778-7727	Phone number: 301-827-1084
Subject: Atrovent HFA Pre-NDA/CMC meeting minutes	

Total no. of pages including cover: 10

Comments:

Document to be mailed: YES NO

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IND 45,938

Drug: ipratropium bromide HFA

Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI)

Pre-NDA/CMC only meeting

Meeting Date: March 27, 2002

IMTS: 8285

Page 1

BIPI representatives:

Burkhard Blank, M.D.	Medical & Drug Regulatory Affairs
George Chen, Ph.D.	Technical Drug Regulatory Affairs
Arne Froemder, Ph.D.	International Project Management
Thomas Hampe, Ph.D.	Research & Development Project Management
Paul Jager, M.S.	Pharmaceutical Sciences
Dan Norwood, Ph.D.	Analytical Sciences
Rajni Patel, M.D.	Analytical Sciences
Jeffrey Snyder	Drug Regulatory Affairs
Terrence Tougas, Ph.D.	Analytical Sciences
Patricia Watson, M.S.	Technical Drug Regulatory Affairs

Division of Pulmonary & Allergy Drug Products (DPADP):

Ladan Jafari	Regulatory Project Manager
Robert Meyer, M.D.	Director
Guirag Poochikian, Ph.D.	CMC Team Leader
Brian Rogers, Ph.D.	CMC Reviewer
Alan Schroeder, Ph.D.	CMC Reviewer

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8 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

IND 45,938

Drug: ipratropium bromide HFA

Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI)

Pre-NDA/CMC only meeting

Meeting Date: March 27, 2002

IMTS: 8285

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Drafted: LJ/4-4-02

Initialed by: Schroeder/4-24-02
Poochikian/4-24-02
Meyer/5-1-02

Filename: Atrovent HFA mtgmin March 27.doc

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/s/

Ladan Jafari
5/1/02 10:18:49 AM

IND 45,938

Drug: Ipratropium bromide inhalation aerosol HFA-134a

Pre-NDA meeting (CMC not included)

Meeting Date: January 16, 2002

IMTS: 8073

Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI)

Burhard Blank, M.D., Clinical Research

George Chen, Ph.D., Drug Regulatory Affairs, CMC

Joachim Coenen, Ph.D., Toxicology

Bernd Disse, M.D., Clinical Research

Nora Fagan, Biometrics & Data Management

Arne Froemder, Ph.D., International Project Management

Mo Ghafouri, Ph.D., Clinical Research

Thomas Hampe, Ph.D., Research & Development, Project Management

Paul Jager, Research & Development

Martin Kaplan, M.D., J.D., Drug Regulatory Affairs

Thomas MacGregor, Ph.D., DMPK

Shailendra Menjuge, Ph.D., Biometrics & Data Management

Thomas Mueller, M.D., Clinical Research

Charles Serby, M.D., Clinical Research

Jeffrey Snyder, Drug Regulatory Affairs

Susan Wang, Ph.D., Biometrics & Data Management

Division of Pulmonary & Allergy Drug Products (DPADP)

Raymond Anthracite, M.D., Medical Reviewer

Young-Moon Choi, Ph.D., Clinical Pharmacology & Biopharmaceutics Reviewer

Donald Collier, Regulatory Project Manager, IT

Emmanuel Fadiran, Ph.D., Clinical Pharmacology & Biopharmaceutics Team Leader

James Gebert, Ph.D., Biometrics Team Leader

Ladan Jafari, Regulatory Project Manager

Marianne Mann, M.D., Deputy Director

Luqi Pei, Ph.D., Preclinical Reviewer

Joe Sun, Ph.D., Supervisory Pharmacologist

Background: BIPI submitted a Pre-NDA meeting request dated October 4, 2001, to discuss ipratropium bromide inhalation aerosol HFA 134a. BIPI submitted a briefing package on December 14, 2001, which contained all the questions to be discussed at this meeting. A separate CMC meeting will be requested by BIPI in the near future. Questions raised by BIPI in their briefing package are printed in *Italics* below, followed by the Division's comments.

CMC:

1. *Is it acceptable to the Division to submit the CMC section in the CTD format while maintaining the overall submission in the FDA format?*

- The Division accepted the proposal.

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Drug: Ipratropium bromide inhalation aerosol HFA-134a

Pre-NDA meeting (CMC not included)

Meeting Date: January 16, 2002

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Preclinical:

2. *Based on the list of studies to be presented in the preclinical section and on their respective brief overview, does the Division concur that adequate pharmacology, toxicology, and non-clinical ADME studies have been conducted to support the filing of this NDA?*
 - The Division agreed that the preclinical program is complete. Issues concerning the drug impurities, degradation products, leachables and extractables will be addressed during the review of the application.

Clinical Pharmacology & Biopharmaceutics:

3. *Based on the list of studies to be presented in the Human Pharmacokinetics and Bioavailability section and on their respective brief overview, does the Division concur that adequate human pharmacokinetic studies have been conducted to support the filing of this NDA?*
 - The Division agreed that the program is complete. The quality of data remains a review issue. The Division stated that they would accept SAS transfer file for presentation of clinical pharmacology data.

Clinical:

4. *Clinical sections submitted in the background package provide the outline of the analysis plans for presentation of data in the ISS and ISE. Does the Division agree with the format for presentation of the data and tables in the ISS and ISE outlines?*
5. *The safety database and overall ISS will include an evaluation of all studies in human subjects who were administered ipratropium bromide. However, the primary focus in the ISS and labeling is based on the two 12-week controlled trials in COPD (244.1405,244.1408) and the one year controlled trial (204.2453). Does the Division have comments or recommendations regarding the proposed strategy for presentation of the safety data in the ISS analysis plans or in the draft labeling?*
6. *The overall ISE will include discussion on all studies that had any efficacy measurements. However, the primary focus in the ISE and labeling will be based on the 12-week placebo/active controlled US study (244.1405). At this time do you have any comments or recommendations regarding the strategy for presentation of efficacy data in the ISE analysis plans or in the labeling?*

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- The Division indicated that all of BIPI's fragmentary safety reporting is acceptable, however, BIPI should also put all safety reporting of Phase 2-3 trials into the following two categories:
 1. All controlled trials by treatment/control (for both COPD and asthma together and separately).
 2. All uncontrolled trials.
- The Division requested that BIPI present safety variables as categorical shift tables at baseline and at the maximum, or minimum value during treatment. (Please refer to Dr. Anthracite's overhead slides in attachment 1).
- The Division also recommended that BIPI integrate all safety reporting within the two above categories; e.g., deaths, SAEs, early D/C, Aes, labs, VS. etc.
- The Division requested that BIPI include a narrative summary for each patient who dies, reports a Serious Adverse Event or terminates early because of an Adverse Event.
- The Division also requested that the electronic submission include hyperlinks to move the reviewer from safety data to the appropriate case report forms. The Division would prefer direct links, which would not require navigating back and forth through intermediate links.

Electronic Submission

7. *Do you concur with our approach of submitting NDA Item 11 (Case Report Tabulations; CRTs) only as SAS datasets in the electronic archival copy? With this approach, CRTs will neither be provided in paper as part of the clinical study reports in the Technical Review Section nor as PDF files.*
8. *Do you concur with our proposal to provide efficacy analysis program, but not safety programs?*
9. *Do you concur with our approach of submitting NDA Item 12 (Case Report Forms, CRFs) only in the electronic archival copy? With this approach, CRFs would not be provided as part of the clinical study reports in the Technical Review Section.*
10. *Do you concur with our approach to hypertext links, which will be to provide hypertext links and bookmarks from the table of contents for PDF documents and only very limited hypertext link in the body of the PDF files. The CRFs (Item 12) will have hypertext links and bookmarks as described in the Electronic Submission Guidance.*

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Drug: Ipratropium bromide inhalation aerosol HFA-134a

Pre-NDA meeting (CMC not included)

Meeting Date: January 16, 2002

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11. *Will FDA be able to work with SAS version 6.12, or will version 8.0 be required or strongly preferred by the time of this submission?*

- The Division agreed with all the above proposals and indicated that we would prefer as many hyperlinks as possible in the electronic submission.
- The Division also requested that BIPI submit a word version as well as a PDF version of the labeling in the archival copy of the electronic submission.
- The Division indicated that we would accept SAS version 6.12.

The Division asked as to when BIPI was planning to submit the NDA application for ipratropium bromide inhalation aerosol HFA-134a. BIPI responded that they are planning to submit this application by the end of the 3rd quarter of 2002.

Ladan Jafari, Regulatory Project Manager

IND 45,938

Drug: Ipratropium bromide inhalation aerosol HFA-134a

Pre-NDA meeting (CMC not included)

Meeting Date: January 16, 2002

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Attachment:

INTEGRATED SAFETY SUMMARY

1. Proposals for data breakdown and presentation are fine,

BUT...PLEASE ADD THE FOLLOWING:

All doses, durations, Phases (2-3) broken down into:

1. Controlled trials, by treatment
2. Uncontrolled trials

This breakdown should be used to integrate all safety reporting within the two above categories; e.g., deaths, SAE's, early D/C, AE's, labs, VS, etc.

CATEGORICAL SHIFT TABLES

For ordinal scale, or higher, safety parameters (WBC, Na⁺, pulse, QTc, etc.), contrast patient counts in mutually exclusive categories of baseline values...

1. greater than markedly elevated (>ME)
2. greater than upper limit of normal, but less than markedly elevated (>ULN)
3. within normal limits (WNL)
4. less than lower limit of normal, but greater than markedly decreased (<LLN)
5. less than markedly decreased (<MD)

...contrasted with maximum and minimum values during treatment.

Say, heart rate, for 100 patients in all controlled Phase 2-3 trials treated with all doses/durations of Atrovent HFA.

MAX. DURING BASELINE	MAXIMUM VALUE DURING TREATMENT					Total
	< MD	< LLN	WNL	> ULN	> ME	
> ME			3	1	1	5
> ULN		1	8	7		16
WNL	2	1	48	11		62
< LLN		2	9	1	1	13
< MD			3		1	4
Total	2	4	71	20	3	

Categorical shifts up from baseline during treatment, are in contiguous shaded cells.

This table will be compared with placebo group, similarly derived and defined.

IND 45,938

Drug: Ipratropium bromide inhalation aerosol HFA-134a

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Say, serum potassium, for 100 patients in all controlled Phase 2-3 trials treated with all doses/durations of Atrovent HFA.

MIN. DURING BASELINE	MINIMUM VALUE DURING TREATMENT					Total
	< MD	< LLN	WNL	> ULN	> ME	
> ME			3	1	1	5
> ULN		1	8	7		16
WNL	2	1	48	11		62
< LLN		2	9	1	1	13
< MD			3		1	4
Total	2	4	71	20	3	

Categorical shifts down from baseline during treatment, are in contiguous shaded cells.

This table will be compared with placebo group, similarly derived and defined.

2. Include a narrative summary for each patient who dies, reports an SAE or terminates early because of an AE.
3. The electronic submission should include hyperlinks to move the reviewer from safety data to the appropriate case report forms. Preferably, these should be direct links and not require navigating back and forth through intermediate links.

IND 45,938

Drug: Ipratropium bromide inhalation aerosol HFA-134a

Pre-NDA meeting (CMC not included)

Meeting Date: January 16, 2002

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Initialed by: Anthracite/1-28-02

Collier/1-24-02

Pei/1-28-02

Sun/1-28-02

Choi/1-28-02

Fadiran/1-28-02

Gebert/1-24-02

Mann/1-30-02

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/s/

Ladan Jafari
1/30/02 01:37:24 PM

Record of Telephone Conversation

Date of Telecon: January 9, 2002
Subject: IND 45,938
Initiated by: Sponsor
Product Name: Ipratropium Bromide Inhalation Aerosol HFA-134a
Firm Name: Boehringer Ingelheim Pharmaceuticals Inc.
Contact: Dr. George Chen, regulatory affairs
Telephone Number: 203-798-4366

Dr. Chen called me to ask about clinically relevant particle sizes for an inhalation drug product. He wanted to know if there was an agreement on this subject between the chemists and clinicians in this Division. He mentioned a change in the valve during development of the above product that resulted in some change in particle size distribution [note that this issue has been previously discussed with this Division]. I said that I could not speak for the clinicians, but my viewpoint was that we don't have enough data to absolutely determine "clinically relevant particle sizes." We want as much of the particle size distribution as possible to be controlled, so that the drug product matches that used in clinical trials. There was a brief discussion of particle sizes less than μm , for which I indicated that there may be an increasing likelihood of particles being exhaled as they become smaller than μm . Even this is not an all or none phenomenon. The behavior of inhaled particles may vary according to their nature (e.g., particle shape) as well as size, which is another reason why we can't give a fixed particle size range of concern.

He said that this information was helpful. He stated that they plan to make a request around the end of January 2002 for a CMC pre-NDA meeting, with the package submitted around the end of February (if not sooner), and a meeting date around the end of March.

Alan C. Schroeder, Ph.D.

<p>cc: Orig. IND # 45,938 HFD-570/Division file HFD-570/ACSchroeder/ HFD-570/GPoochikian HFD-570/CSO LJafari</p>	<p>R/D init. by: F/T by: ACSchroeder/1-10-2002 ACSfile: I45938_2002-01-09.doc</p>
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/s/

Alan Schroeder
1/10/02 12:29:29 PM
CHEMIST

telecon memo

Guiragos Poochikian
1/10/02 04:24:54 PM
CHEMIST