

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-457

ADMINISTRATIVE
DOCUMENTS/CORRESPONDENCE

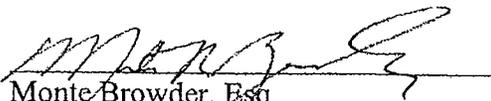
1.2.2 Patent Certification and Patent Listing Information**PARAGRAPH IV PATENT CERTIFICATION**

In accordance with Section 505(b)(2)(A)(iv) of the Federal Food, Drug and Cosmetic Act and 21 CFR Part 314.54(a)(1)(vi), IVAX Research, Inc. certifies that the following patents listed for Proventil® HFA will not be infringed upon by the manufacture, use or sale of IVAX's Volare™ HFA (Albuterol Sulfate, USP) Inhalation Aerosol, for which this application is submitted:

- U.S. Patent No. 5225183 – Expiry date: July 06, 2010
- U.S. Patent No. 5439670 – Expiry Date: July 06, 2010
- U.S. Patent No. 5605674 – Expiry Date: February 25, 2014
- U.S. Patent No. 5766573 – Expiry Date: June 16, 2015
- U.S. Patent No. 6352684 – Expiry Date: November 28, 2009
- U.S. Patent No. 5695743 – Expiry Date: July 6, 2010

We will comply with the notification requirements defined in Section 505(b)(3)(A) and (B), of the Federal Food, Drug, and Cosmetic Act, (Codified at 21 CFR Part 314.52(a), and the content of our notice will conform to the requirements defined in 505(b)(3)(B) (Codified at 21 CFR Part 314.52(c)) and such notice will be addressed to the owner of the listed patents and the holder of the approved application as required by 505(b)(3)(A).

IVAX Research, Inc. intends to market its Albuterol HFA MDI upon a approval of this application.


Monte Browder, Esq.
Deputy General Counsel

1/29/03 (4/3/03)
Date

1.2.1 Patent Information

Based upon information published in the “Approved Drug Products with Therapeutic Equivalence Evaluations” (“Orange Book”), 22nd Edition, including the Electronic Orange Book through February, 2003 and the Patent Term Extension and New Patents Docket Number *95S-0117 published January 24, 2003 and current through March 28, 2003 (copies provided), the following patents are listed for Proventil-HFA and held by 3M Pharmaceuticals.

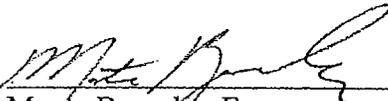
- U.S. Patent No. 5225183 – Expiry Date: July 06, 2010
- U.S. Patent No. 5439670 – Expiry Date: July 06, 2010
- U.S. Patent No. 5605674 – Expiry Date: February 25, 2014
- U.S. Patent No. 5766573 – Expiry Date: June 16, 2015
- U.S. Patent No. 6352684 – Expiry Date: November 28, 2009
- U.S. Patent No. 5695743 – Expiry Date: July 6, 2010

There are no unexpired marketing exclusivities in effect for Proventil-HFA.

EXCLUSIVITY STATEMENT

Based upon information published in the *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"), 22nd Edition, (including the Electronic Orange Book, current through February, 2003 and the Patent Term Extension and New Patents Docket Number *95S-0117 published January 24, 2003 and current through March 28, 2003, the reference listed drug currently is not entitled to marketing exclusivity.

IVAX Research, Inc. intends to markets its Volare™ HFA (Albuterol Sulfate, USP), Inhalation Aerosol upon approval of this NDA.



Monte Browder, Esq.
Deputy General Counsel

1/29/03 (4/3/03)
Date

EXCLUSIVITY SUMMARY FOR NDA # 21-457

SUPPL # _____

Trade Name _____

Generic Name **albuterol sulfate**

Applicant Name **IVAX Research**

HFD # **570**

Approval Date If Known **October 29, 2004**

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 // NO /___/

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

505 (b) (2)

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 // 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:

- d) Did the applicant request exclusivity?

NDA# 20-503 Proventil HFA

NDA# 20-983 Albuterol HFA

NDA# 20-949 AccuNeb

NDA# 20-950 DuoNeb

NDA# 20-291 Combivent

In addition, there are several other NDA and ANDA's and many generic drug products.

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."

conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /X/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

BNP-301-4-167

BNP 301-4-105

IX-105-105

IX-100-105.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency

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 #1-4 !

IND # 60, 549 YES /**X**/ ! NO /___/ Explain: _____

!
!

Investigation #2 !

IND # _____ 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 _____

!
!
!
!
!

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /**X**/

**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
10/29/04 05:18:02 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-457 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: January 30, 2003, Resubmission April 29, 2004 Action Date: October 31, 2004

HFD-570 Trade and generic names/dosage form:

Applicant: IVAX Research, Inc. Therapeutic Class:

Indication(s) previously approved:

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

Number of indications for this application(s): one

Indication #1: treatment or prevention of bronchospasm with reversible obstructive airway disease in adults and children 12 years of age and older

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

- Yes: Please proceed to Section A.
- No: Please check all that apply: ___ Partial Waiver X Deferred X 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: MDIs not practical in children less than 4 years of age.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

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.

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

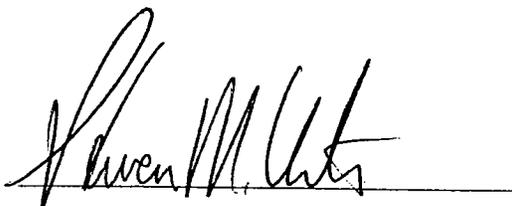
/s/

Akilah Green

11/1/04 02:05:21 PM

1.2.3 Debarment Certification**Section 306(k)(1) Requirement**

IVAX Research, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application for Volare™ HFA (Albuterol Sulfate, USP) Inhalation Aerosol.



Steven M. Viti, Ph.D.
Director, Regulatory Affairs

1/30/03 (5/12/03)

Date

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-457	Efficacy Supplement Type SE-	Supplement Number
Drug: Volare HFA (albuterol sulfate, USP) Inhalation Aerosol		Applicant: IVAX
RPM: Akilah Green		HFD- 570 Phone # 827-5580
Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name): Proventil HFA
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		
• Other (e.g., orphan, OTC)		
❖ User Fee Goal Dates		November 30, 2003
❖ 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
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		
• OC clearance for approval		
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that patent information was submitted		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input checked="" type="checkbox"/> IV 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input checked="" type="checkbox"/> Verified
❖ Exclusivity Summary (approvals only)		
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)		

General Information	
❖ Actions	
• Proposed action	<input type="checkbox"/> AP <input type="checkbox"/> TA <input checked="" type="checkbox"/> AE <input type="checkbox"/> NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	<input 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 checked="" 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)	
• Most recent applicant-proposed labeling	None
• Original applicant-proposed labeling	January 31, 2003
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (<i>indicate dates of reviews and meetings</i>)	October 23, 2003
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	November 8, 2001, November 14, 2001
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	

Clinical and Summary Information

❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	
❖ Clinical review(s) (indicate date for each review)	11/24/03, 4/2/03
❖ Microbiology (efficacy) review(s) (indicate date for each review)	NA
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	Pg 40 - 11/24/03 Rev
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	NA
❖ Statistical review(s) (indicate date for each review)	10/20/03
❖ Biopharmaceutical review(s) (indicate date for each review)	10/24/03
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	NA
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	November 12, 2003
• Bioequivalence studies	

CMC Information

❖ CMC review(s) (indicate date for each review)	
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	
• Review & FONSI (indicate date of review)	
• Review & Environmental Impact Statement (indicate date of each review)	
❖ Micro (validation of sterilization & product sterility) review(s) (indicate date for each review)	
❖ Facilities inspection (provide EER report)	Date completed: () Acceptable () Withhold recommendation
❖ Methods validation	() Completed () Requested () Not yet requested

Nonclinical Pharm/Tox Information

❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	November 14, 2003
❖ Nonclinical inspection review summary	NA
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	NA
❖ CAC/ECAC report	NA

NDA 21-457

Regulatory Project Management Labeling Review

IVAX submitted draft labeling for their new drug application for NDA 21-457, [TRADE NAME] (albuterol sulfate) Inhalation Aerosol, on April 29, 2004. The labeling provided for the use of albuterol sulfate HFA Inhalation Aerosol for the treatment or prevention of bronchospasm with reversible obstructive airway disease in adults and children 12 years of age and older.

The labeling was reviewed by the Clinical, Chemistry, Manufacturing, and Controls, Pharmacology/Toxicology, Clinical Pharmacology and Biopharmaceutics, and Statistical teams. Labeling changes were sent to IVAX by facsimile correspondence on October 14, and 26, 2004, and IVAX accepted all of the labeling changes.

IVAX submitted revised draft labeling dated October 28, 2004, for the Package Insert, Patient Leaflet, and carton and container. I compared the draft labeling dated October 28, 2004, to the Division's requested labeling changes dated October 21, and 26, 2004. The revised draft labeling is identical to the Division's labeling suggestions with exception of minor formatting. In addition, in the _____ of the carton and container, _____ should be changed to _____, this is consistent with the language in the Package Insert and the Patient Leaflet. Also, the first paragraph in parenthesis of the Carcinogenesis, Mutagenesis and Impairment to Fertility section of the Package Insert should be changed to "_____" I discussed this with IVAX by telephone on October 29, 2004, and IVAX agreed to make the changes.

Upon review of the labeling by the Clinical, Chemistry, Manufacturing, and Controls, and Project Management Teams, we agreed with the labeling changes submitted October 28, 2004, with the exception of the change to the _____ of the carton and container.

The draft labeling dated October 28, 2004, should be approved.

Akilah Green
Regulatory Project Manager
Division of Pulmonary and Allergy Drug Products

IVAX Research Inc.
4400 Biscayne Blvd.
Miami Fl 33137
Telephone 305 575 6000

FAX 305 575 6339

FAX TRANSMISSION FORM

DATE: October 29, 2004
TO: Akilah Green FAX301 827 1271
FROM: John Lay 
RE: NDA 21-457 (Albuterol MDI – Insert revised)

NUMBER OF PAGES INCLUDING COVER SHEET:

MESSAGE:

Akilah, as discussed, we will be changing the package insert subsection *Carcinogenicity, Mutagenesis and Impairment of Fertility* first paragraph, last sentence to read

**APPEARS THIS WAY
ON ORIGINAL**

IVAX Research, Inc.
4400 Biscayne Blvd.
Miami, Florida 33137
Telephone: (305) 575-6000

FAX: 305-575-6339
FAX TRANSMISSION FORM

DATE: October 29, 2004
TO: Akilah Green FAX: 301-827-1271
FROM: John Lay 
RE: NDA 21-457 (Albuterol MDI) - Labeling (revised)

NUMBER OF PAGES INCLUDING COVER SHEET:

MESSAGE:

Akilah, as discussed, we will change the _____ on the side panel of the carton to read: _____

Thank you.

**APPEARS THIS WAY
ON ORIGINAL**

IVAX Research, Inc.
4400 Biscayne Blvd.
Miami, Florida 33137
Telephone: (305) 575-6000

FAX: 305-575-6339
FAX TRANSMISSION FORM

DATE: October 29, 2004
TO: Akilah Green FAX: 301-827-1271
FROM: John Lay 
RE: NDA 21-457: Albuterol HFA MDI

NUMBER OF PAGES INCLUDING COVER SHEET: 1

MESSAGE:

Akilah, as discussed in our telephone conversation this morning, IVAX agrees to the following request:

1. Page 2 of our communication of October 27, 2004 concerning APSD groupings: IVAX agrees with the following change:

“IVAX will propose an alternate approach to this test as a Prior Approval Supplement post-approval.”

Thank you for getting this finalized for us.

**APPEARS THIS WAY
ON ORIGINAL**



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

FACSIMILE TRANSMITTAL SHEET

Date: October 29, 2004

To: John Lay Associate Director, Regulatory Affairs	From: Akilah Green Regulatory Project Manager
Company: IVAX	Division of Pulmonary and Allergy Drug Products
Fax number: 305-575-6339	Fax number: 301-827-1271
Phone number: 305-575-6337	Phone number: 301-827-5585

Subject: NDA 21-457 Approval Letter

Total no. of pages including cover: 22

Comments:

Document to be mailed: XYES 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.

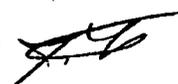
If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please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

FAX

IVAX Research, Inc.
REGULATORY AFFAIRS

Date: <u>October 28, 2004</u>
Number of pages including cover sheet: <u>1</u>

To: Akilah Green
Phone: _____
Fax phone: <u>301-827-1271</u>

From: John Lay 
Phone: <u>305-575-6337</u>
Fax phone: <u>305-575-6339</u>

REMARKS: <input checked="" type="checkbox"/> Urgent <input type="checkbox"/> For your review <input checked="" type="checkbox"/> Reply ASAP <input type="checkbox"/> Please comment
<p>RE: <u>NDA 21-457</u></p> <p>Akilah,</p> <p>The purpose of this fax is to confirm your request from our teleconference today. Reference is made to our submission dated October 27, 2004.</p> <ol style="list-style-type: none"> Page 2 – IVAX agrees with the following change: “It is agreed that IVAX would propose an alternate approach to this test as a Prior Approval supplement post-approval” As requested “LC” will be added to % (i.e. % LC) Mass Balance as presented on Page 2 and on Regulatory Finished Product Specification (Page 2 of 54). As requested “Carton and Container” labeling will be e-mailed to you and will also be sent via FedEx this evening. <p>We will follow up this fax with a hard copy to NDA 21-457.</p> <p>Thanks for your assistance.</p>

IVAX Research, Inc.
4400 Biscayne Blvd.
Miami, Florida 33137
Telephone: (305) 575-6000

FAX: 305-575-6339
FAX TRANSMISSION FORM

DATE: October 27, 2004
TO: Akilah Green FAX: 301-827-1271
FROM: Jackie Howard *Howard*
RE: Albuterol MDI NDA 21-457

NUMBER OF PAGES INCLUDING COVER SHEET: 18

MESSAGE:

Akilah, attached are the labeling changes per your fax of October 26, 2004. This is also being e-mailed to you, and a hard copy will be submitted formally to the NDA on CD.

IVAX Research, Inc.
4400 Biscayne Blvd.
Miami, Florida 33137
Telephone: (305) 575-6000

FAX: 305-575-6339
FAX TRANSMISSION FORM

DATE: October 26, 2004

TO: Akilah Green FAX: 301-827-1271

FROM: Steve Viti

RE: NDA 21-457: Albuterol MDI – Response to CMC Comments

NUMBER OF PAGES INCLUDING COVER SHEET: 4 (5)

MESSAGE:

Akilah, based on our teleconference today, attached is our response to all remaining unresolved items. This is being submitted formally to the NDA today.

Thank you.



IVAX**IVAX Research, Inc.**

4400 Biscayne Boulevard

Miami, Florida • 33137

Telephone: 305-575-6000

October 26, 2004

Badrul Chowdhury, M.D.
 Director, Division of Pulmonary Drug Products
 Food and Drug Administration
 Center for Drug Evaluation and Research (HFD-570)
 Attention: Document Control Room 8B-45
 5600 Fishers Lane
 Rockville, MD 20857

Re: **NDA 21-457: Albuterol Sulfate Inhalation Aerosol (Albuterol MDI)**

Correspondence

Dear Dr. Chowdhury:

Reference is made to our NDA 21-457 for Albuterol HFA MDI Inhalation Aerosol 90 mcg submitted January 30, 2003. Reference is also made to the comments from the Agency dated October 21, 2004 containing CMC issues to be resolved prior to approval, to the teleconference the next day, and to our formal response submitted October 25, 2004. Reference is also made to the five CMC comments received October 26, 2004 and to the teleconference that followed later that same day to discuss those comments as well as Comment #3 (leachables specification) from the Friday, October 21, 2004 comments. Following is our response to all unresolved issues.

Leachables:

In today's teleconference, the Agency proposed specifications of NMT _____ for the _____ FDA advised these levels are acceptable to proceed, but must be qualified post approval of the product.

IVAX agrees to accept the levels of NMT _____ for the _____ Within two months of approval, IVAX will submit supportive information for these limits and/or a protocol to conduct a 90-day animal toxicology study to qualify these levels if available information is not sufficient. If, after review of the supportive information the Agency decides it is not sufficient and that it will be necessary to conduct the 90-day study in animals, we commit to conducting the animal study and submitting the final report to the Division within 9 months after FDA feedback on the study is received.

C O N F I D E N T I A L

IVAX Research, Inc. 4400 Biscayne Boulevard • Miami, Florida • 33137

Batch Manufacturing Record (From Tuesday, October 26, 2004 and Thursday, October 21, 2004):

1. (Tuesday, October 26, 2004): The detailed specifics of the _____ should include not only the validated ranges for the _____ as specified in validation report 03-AVR-012 (Appendix 10, 100149).

See response to Comment 8 below.

8. (Thursday, October 21, 2004): Confirm that _____ testing is applied to _____ (manufactured product). Revise the MBR to include detailed specifics of the _____. Additionally, provide the number and percentage of _____ resulted from the _____ that were not subjected to _____.

On Monday, October 25, 2004, IVAX responded that we confirm that _____ testing is applied to _____ (manufactured product). IVAX provided the following table of _____ Rejects from the _____.

With regard to the balance of comments from Thursday, October 21 and Tuesday, October 26, 2004, IVAX confirms that the MBR will be revised on page 12/24 of AMR 613/13 to specify that _____ testing is applied _____ on page 12/24 of _____. Further, in addition to the validated ranges for the _____ which already appear on the document, _____ will be further revised to specify a _____. This revised document will be submitted to the Agency before close of business Thursday, October 28, 2004.

Comments from Tuesday, October 26, 2004:

2. Prior to modifying the APSD test methodology to test only beginning of inhaler for the commercial batches, agree to provide supportive data demonstrating the absence of discernible within-unit APSD trends from beginning to end of inhaler throughout shelf life the Agency's evaluation. Additionally, note that, if deemed necessary, the Agency may revisit the appropriateness of the APSD acceptance criteria on the basis of evaluation of the stability data provided in support of the expiration dating extension.

For the commercial batches, prior to modifying the APSD test methodology to test only beginning of inhaler for the commercial batches IVAX commits to providing supportive data demonstrating the absence of discernible within-unit APSD trends from beginning to end of inhaler throughout shelf life for the Agency's evaluation. IVAX also notes that the Agency may revisit the appropriateness of the APSD acceptance criteria on the basis of evaluation of the stability data provided in support of the expiration dating extension.

3. In the absence of any comparable data between the valve delivery results from incoming valve lots and the valve delivery results from the drug product batches at release, perform valve delivery (shot weight) testing for the drug product until such data are made available for Agency's evaluation. You may submit such supportive data post-approval, if you wish to substitute release testing of valve delivery for the drug product with acceptance testing for valve delivery on incoming valve lots from the valve supplier.

IVAX commits to performing valve delivery (shot weight) testing for the drug product and collecting the data to submit post-approval, as indicated above. We will continue to perform acceptance testing for valve delivery on incoming valve lots from the valve supplier until such time as the substitution is made.

4. Revise the stability protocol to include valve delivery (shot weight) as one of the test parameters. Requirements for valve testing at stability may be reduced (e.g., to skip-lot testing), provided that the valve delivery results from stability testing are found to be statistically comparable to valve results from release testing of the drug product and are provided for the Agency's evaluation.

IVAX commits to revising the stability protocol to include valve delivery (shot weight) as one of the test parameters. We acknowledge the Agency's comment that requirements for valve testing at stability may be reduced (e.g., to skip-lot testing), provided that the valve delivery results from stability testing are found to be statistically comparable to valve results from release testing of the drug product and are provided for the Agency's evaluation.

In addition, as requested in the Agency's comments of October 21, 2004, the stability protocol will be revised for leachables testing to be performed initially, annually and at expiry until the correlation between leachables and extractables has been established and evaluated by the Agency. Further, Table 1 of the stability protocol submitted in our March 15, 2004 Major Amendment (Appendix 17) will be revised to specify all time points as _____

C O N F I D E N T I A L

IVAX Research, Inc. 4400 Biscayne Boulevard • Miami, Florida • 33137

3. The revised stability protocol submitted to the Agency before close of business Thursday, October 28, 2004.

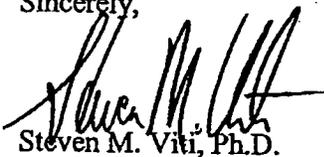
5. Confirm that the acceptance criteria proposed for total *impurities/degradation products* in the drug product are also inclusive of the drug substance impurities, which are controlled at the drug substance level.

IVAX confirms that the acceptance criteria proposed for *total impurities/degradation products* in the drug product are also inclusive of the drug substance impurities, which are controlled at the drug substance level.

We believe the above responds to all issues identified by the Agency in their fax communications of October 21, 2004 and October 26, 2004 and to the teleconference discussions and agreements between us. We thank the Division for their thoughtful comments and guidance, and we confirm that updated drug product specification — batch record documentation AMR 613/18 (page of 26) and stability protocol will be submitted to the Agency by Thursday, October 28, 2004.

Please note that a copy of this response is being submitted to the Field Office. Should you have any questions or comments, please call me or John Lay at (305) 575-6337 or via fax to 305-575-6339 should you have any questions.

Sincerely,



Steven M. Viti, Ph.D.

Senior Director, Regulatory Affairs

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IVAX Research, Inc. 4400 Biscayne Boulevard • Miami, Florida • 33137



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

FACSIMILE TRANSMITTAL SHEET

DATE: October 26, 2004

To: John Lay, RAC Associate Director, Regulatory Affairs	From: Akilah Green Regulatory Project Manager
Company: IVAX Research, Inc	Division of Pulmonary and Allergy Drug Products
Fax number: 305-575-6339	Fax number: 301-827-1271
Phone number: 305-575-6337	Phone number: 301-827-5585

Subject: NDA 21-457 Labeling comments

Total no. of pages including cover: 21

Comments: Make sure the indents are the same throughout the document

Document to be mailed: YES NO

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NDA 21-457
albuterol sulfate HFA Inhalation Aerosol

We have reviewed your draft labeling for the Package Insert and Patient Information Leaflet, submitted to NDA 21-457 dated October 19, 2004, and we have the following comment:

Submit revised draft labeling incorporating the attached revisions.

If you have any questions, please contact Akilah Green, Regulatory Project Manager, at 301-827-5585. Thank you.

Akilah Green, Regulatory Project Manager

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

/s/

Akilah Green

10/26/04 02:32:13 PM .

CSO



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

FACSIMILE TRANSMITTAL SHEET

DATE: October 26
, 2004

To: John Lay Associate Director Regulatory Affairs	From: Akilah Green, Regulatory Project Manager
Company: IVAX Research	Division of Pulmonary and Allergy Drug Products
Fax number: 305-575-6339	Fax number: 301-827-1271
Phone number: 35-575-6337	Phone number: 301-827-5585

Subject: NDA 21-457 CMC comments

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES xNO

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NDA 21-457
Albuterol sulfate HFA Inhalation Aerosol

Comment 1

page # is

100173

Your submission dated March 15, 2004, to NDA 21-457, is current
the following comments:

Additional Issues to be resolved prior to Approval:

1. The detailed specifics of the ' _____ ' should include not only the validated ranges for the _____ specified in validation report 03-AVR-012 (Appendix 10, p 100149) p 100173
2. Prior to modifying the APSD test methodology to test only beginning of inhaler for the commercial batches, agree to provide supportive data demonstrating the absence of discernible within-unit APSD trends from beginning to end of inhaler throughout shelf life for the Agency's evaluation. Additionally, note that, if deemed necessary, the Agency may revisit the appropriateness of the APSD acceptance criteria on the basis of evaluation of the stability data provided in support of the expiration dating extension.
3. In the absence of any comparable data between the valve delivery results from incoming valve lots and the valve delivery results from the drug product batches at release, perform valve delivery (shot weight) testing for the drug product until such data are made available for Agency's evaluation. You may submit such supportive data post-approval, if you wish to substitute release testing of valve delivery for the drug product with acceptance testing for valve delivery on incoming valve lots from the valve supplier.
4. Revise the stability protocol to include valve delivery (shot weight) as one of the test parameters. Requirements for valve delivery testing at stability may be reduced (e.g., to skip-lot testing), provided that the valve delivery results from stability testing are found to be statistically comparable to valve delivery results from release testing of the drug product and are provided for the Agency's evaluation.
5. Confirm that the acceptance criteria proposed for *total impurities/degradation products* in the drug product are also inclusive of the drug substance impurities, which are controlled at the drug substance level.

If there are any questions, please contact Akilah Green, Project Manager, at 301-827-5585.

Akilah Green, Regulatory Project Manager

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/s/

Akilah Green
10/26/04 10:35:01 AM
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___ § 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: October 21, 2004

To: John Lay Associate Director Regulatory Affairs	From: Akilah Green, Regulatory Project Manager
Company: IVAX Research	Division of Pulmonary and Allergy Drug Products
Fax number: 305-575-6339	Fax number: 301-827-1271
Phone number: 305-575-6337	Phone number: 301-827-5585

Subject: NDA 21-457 CMC comments

Total no. of pages including cover: 4

Comments:

Document to be mailed: YES xNO

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Tier 2:

Test additional — inhalers Beginning and End of life for each Inhaler

NMT — results outside of —

None outside of —

Mean of — results within —

3. Limit the acceptance criteria for the leachable —
— in the drug product to — (equivalent to a maximum daily patient exposure of —) or provide adequate qualification data to support the proposed specifications. If a new toxicology study is deemed to be necessary, the duration of study should be at least 90 days, the route of administration should mimic that proposed for clinical use and the acceptance criteria should be set based upon the no observed adverse effect level (NOAEL).
4. Lower — acceptance criteria, e.g., NMT — at release and NMT — at stability.
5. Revise the stability protocol for leachable testing to be performed initially, annually and at expiry until the correlation between leachables and extractables has been established and has been evaluated by the Agency. All time points in the table 1 should be specified as: — (appendix 17).
6. Based on our evaluation of the — “supportive and bridging” stability data on — and — stability data on — (manufactured with to-be marketed commercial manufacturing process) for critical drug product performance attributes (e.g., DCU and APSD), *no more than 15 months* of expiration dating period (as opposed to requested —) can be granted at this time for the drug product when stored up to 25°C.

You may extend the expiration dating period beyond 15 months by a post-approval submission, once stability data for the first three commercial batches of the drug product are available to support such an extension with real-time data using the approved stability protocol.
7. Perform testing for — and related substances and degradation products routinely on release and during the stability as part of drug product specification. Your proposal to use skip lot testing for these two attributes is not acceptable at this time.
8. Confirm that — testing is applied to — (manufactured product). Revise the — to include detailed specifics of the —
Additionally, provide the number and percentage of all — rejects

Akilah Green, Regulatory Project Manager

**APPEARS THIS WAY
ON ORIGINAL**

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ON ORIGINAL**

IVAX Research, Inc.
4400 Biscayne Blvd.
Miami, Florida 33137
Telephone: (305) 575-6000

FAX: 305-575-6339
FAX TRANSMISSION FORM

DATE: October 20, 2004
TO: Akilah Green FAX: 305-575-1271
FROM: John Lay 
RE: Withdrawal of July 20, 2004 Amendment

NUMBER OF PAGES INCLUDING COVER SHEET: 2

MESSAGE:

Akilah, attached is a copy of the letter we are submitting formally to the NDA today.

Thank you for helping us straighten this out.

**APPEARS THIS WAY
ON ORIGINAL**



October 20, 2004

IVAX Research, Inc.4400 Biscayne Boulevard
Miami, Florida • 33137
Telephone: 305-575-6000

Badrul Chowdhury, M.D.
Director, Division of Pulmonary Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-570)
Attention: Document Control Room 8B-45
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-457 Albuterol Sulfate, USP Inhalation Aerosol**Withdrawal of July 20, 2004 Amendment**

Dear Dr. Chowdhury:

Reference is made to our NDA 21-457 for Albuterol HFA MDI Inhalation Aerosol 90 mcg (Albuterol HFA MDI). Reference is also made to our Amendment of October 20, 2003 submitting samples of the product, comprised of a blue actuator with dark blue dustcap and our Amendment of July 20, 2004 informing the Agency that we would be

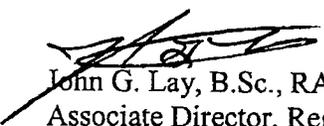
As discussed with Ms. Akilah Green, Project Manager, today, and as noted in our correspondence of October 18 and 19, 2004, IVAX no longer wishes to

IVAX has reverted to its original plan, and the color of the actuator at commercial launch will be blue. We therefore wish to withdraw our Amendment of July 20, 2004, and we apologize for any confusion.

This will also confirm that all stability and clinical studies conducted for this application utilized the blue actuator and that the DMF which was reviewed by the Agency on behalf of this application, contained full information on the blue actuator. It is important to note that at no time has any analytical data on the finished product been submitted to this application: all release and stability data submitted and reviewed has been on the blue device.

We thank the Agency for their help in getting this clarified. Should you have any questions or concerns, please contact me at (305) 575-6337 or via fax to 305-575-6339 or via e-mail to john_lay@ivax.com.

Sincerely,



John G. Lay, B.Sc., RAC
Associate Director, Regulatory Affairs

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IVAX Research, Inc. 4400 Biscayne Boulevard • Miami, Florida • 33137



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

FACSIMILE TRANSMITTAL SHEET

Date: October 14, 2004

To: Terry Duffield	From: Akilah Green Regulatory Project Manager
Company: IVAX Research, Inc	Division of Pulmonary and Allergy Drug Products
Fax number: 305-575-6339	Fax number: 301-827-1271
Phone number: 305-575-6335	Phone number: 301-827-5585
Subject: NDA 21-457 draft labeling comments	

Total no. of pages including cover: 25

Comments:

Document to be mailed: YES X NO

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NDA 21-457

Albuterol Sulfate HFA Inhalation Aerosol

We have reviewed your proposed PI and Patient leaflet, and have the following comments. Note that there are several locations where we have asked you to supply new data points or new information. Also note that the line numbers below refer to the document with the Microsoft Word track changes balloon feature turned off. With Word set in this view, additions and deletions are clearly demarcated, but comments do not show up as clearly demarcated.

Comments regarding the PI:

1. We have made a number of formatting changes to your document to improve readability.
2. To be consistent with other albuterol HFA products, we have added HFA to the product name. *Insert* your new trade name where indicated.
3. The _____ are different than your specifications. Therefore, we have removed the _____ from the wording.
4. We have updated numbers in the appropriate Preclinical, Carcinogenesis, Pregnancy, and Overdosage sections, as well as in the section after the How Supplied section.
5. To match other labeling formats, we have removed several paragraphs from the Preclinical section.
6. We have removed the term " _____" from the Pharmacokinetics and Clinical Trials sections. The term is _____ the _____ . *Remove* the term _____ from the two figures on lines 133 and 135.
7. We have altered the wording in the Clinical Trails section to reflect that the primary comparison in the pivotal study was to placebo, but that an active comparator arm was included.
8. Regarding lines 118-22 of the Clinical Trials section: Your study protocol defined the responder analysis by a change of 15% in FEV1, whereas a 12% increase was a post-hoc analysis _____ .
Replace: _____ , mean, and *insert* numbers for mean time to peak effect and mean duration of effect.
9. We have added lines 234-6 to the Drug Interactions section. While this wording is _____ We feel that this information is useful information regarding drug interactions.
10. Regarding the Nursing Mothers section: For clarity, in the paragraph starting on line 323, we moved the sentence that was at the end of the paragraph to the beginning.
11. We have added appropriate geriatric wording to the Geriatrics section on lines 335-45.
12. We have made the following modifications to the Adverse Reactions section:

- a. We have removed _____
- b. We have removed information _____ *Insert* the number of subjects treated with the IVAX albuterol MDI drug product. _____
- c. We have moved the adverse event table to immediately after the described study.
- d. We have removed paragraphs _____

_____ /
_____ /
_____ This adverse event information does not add any further value to the adverse event information that is present in the label.

- e. We have removed paragraphs referring to _____
This adverse event information does not add any further information to the adverse event information that is present in the label.
13. In the Dosage and Administration section, for clarity we have changed the order of paragraphs and re-worded lines 458-66.
14. Several paragraphs in the How Supplied section and the sections that follow have been reworded. The wording in these sections was updated to closely approximate analogous sections of the Patient leaflet.

Comments regarding the Patient leaflet:

- 1. As in the PI, and to be consistent with other albuterol HFA products, we have added HFA to the product name. *Insert* your new trade name where indicated.
- 2. As in the PI, the _____ are different than your specifications. Therefore, we have removed the _____ from the wording.
- 3. We have made some minor modifications to the wording, and updated numbers in the Storage section.
- 4. We have changed the indents for the cleaning instructions, which should be within bullet #7.
- 5. In Figure C, *replace* “ _____ with “Not clogged.” The two terms are not synonymous. Note that we have placed this comment within the document; the comment should be removed once you have substituted a new figure.
- 6. We have updated the wording of the Warnings section to closely approximate analogous sections of the PI.

Page 3

NDA 21-457

If you have any questions, please contact Ms. Akilah Green, Regulatory Project Manager,
at 301-827-5585.

Akilah Green, Regulatory Project Manager

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/s/

Akilah Green
10/14/04 03:15:47 PM
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C

Admin 16

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✓ § 552(b)(5) Deliberative Process

 § 552(b)(4) Draft Labeling

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

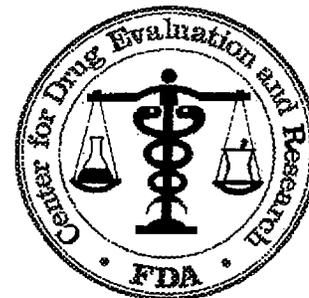
DATE: 24-JUN-2004

TO: Vibhakar Shah, Ph.D.
Chemistry Reviewer
Division of Pulmonary Drug Products (HFD-570)

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

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

SUBJECT: Preliminary Review of 29-APR-2004, 14-APR-2004, 02-APR-2004, and 15-MAR-2004, Amendments in response to 28-NOV-2003, AE letter (assigned 09-JUN-2004)



APPLICATION:

N21-457 Volare® HFA (albuterol sulfate) Inhalation Aerosol from IVAX Research, Inc.

LAST ACTION: Approvable letter of 28-NOV-2003

COMPLETENESS OF RESPONSE:

The review team made the determination that the original response of 15-MAR-2004, was not complete since the DMFs () were not amended in response to the associated deficiencies sent for these files. It was determined that the holder had submitted the information to a new DMF — The applicant sent a letter of authorization for our review of DMF — the 02-APR-2004, amendment. However, due to the possible duplication of our previous efforts regarding the review of DMFs — i, the DMF holder — was informed that they should submit the responses to our deficiency letters regarding the components used by IVAX to the originally referenced DMFs (— . The 14-APR-2004, amendment was a withdrawal of the 02-APR-2004, amendment that provided the LOA for the new DMF — The 29-APR-2004, amendment indicated that the holder of DMF — had responded as of 29-APR-2004. The applicant was informed by letter that we now considered that the 15-MAR-2004, amendment, as further amended by the 29-APR-2004, amendment, a complete response.

STATUS AND REQUEST FOR DMFs:

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

<u>DMF #</u>	<u>Type</u>	<u>Holder</u>	<u>Item Referenced</u>	<u>Reviewer/Date</u>
/	III	/	/	P. Peri/25-NOV-2003
	III			P. Peri/20-NOV-2003
	III			P. Peri/11-NOV-2003

The holder for DMFs _____ claims in their respective 28-APR-2004, amendments to these files that they are provided in response to the Agency deficiency letters generated from the above reviews. However, it was noted that these were not in the typical point-by-point presentation expected in response to an action or deficiency letter. The PM contacted the holder _____ by electronic mail on 23-JUN-2004 asking for a more reviewer-friendly response to our deficiency letters. The holder acknowledged the request and stated that they would review the files and contact the PM “shortly.”

SCOPE OF PRELIMINARY REVIEW:

This preliminary review has graded the responses into five categories of decreasing importance: 1) critical issues requiring resolution prior to approval; 2) non-critical issues for which the applicant response is clearly deficient; 3) non-critical issues for which the applicant has provided more data supporting the currently proposed CMC or where justification for not complying with the Agency request is provided; 4) non-critical issues where it is evident that the applicant’s response satisfies the requests included in the action letter; 5) non-critical issues that should be reviewed in conjunction with information in a DMF. These will be addressed in order below.

INITIAL ASSESSMENT OF RESPONSES REGARDING CRITICAL CMC ISSUES:

1) Critical Issues

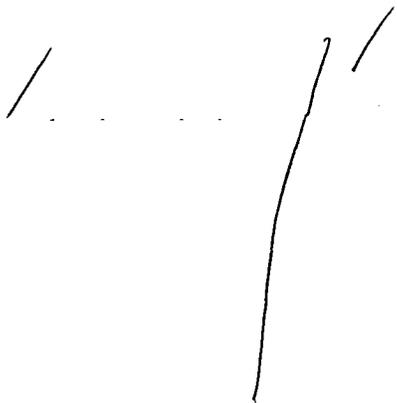
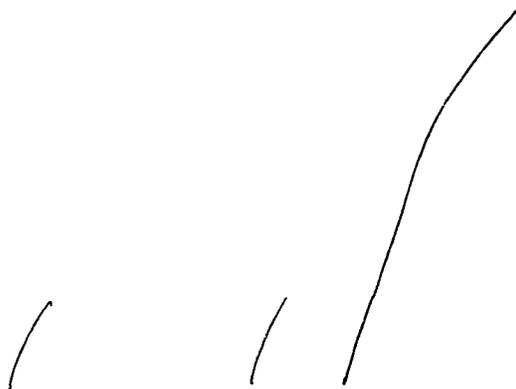
Based on this preliminary review of the applicant’s response, there are, in my opinion, six critical issues for this application that should be addressed first during the review and which may need to be the subject of IR letter comments. These six issues are listed below with their associated AE letter comment designations:

- Particle size distribution of micronized drug substance [1a(2)].
- _____ .c, 2f(8)]

- Leachables/extractables controls [2d(3)]
- Lack of specification for drug product foreign particulates [2d(4)]
- Aerodynamic particle size distribution of the drug product [2d(8)]
- Revision of dose content uniformity (DCU) acceptance criteria [2d(10), 2f(10)(b)]

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

Agency Comment 1a(2)



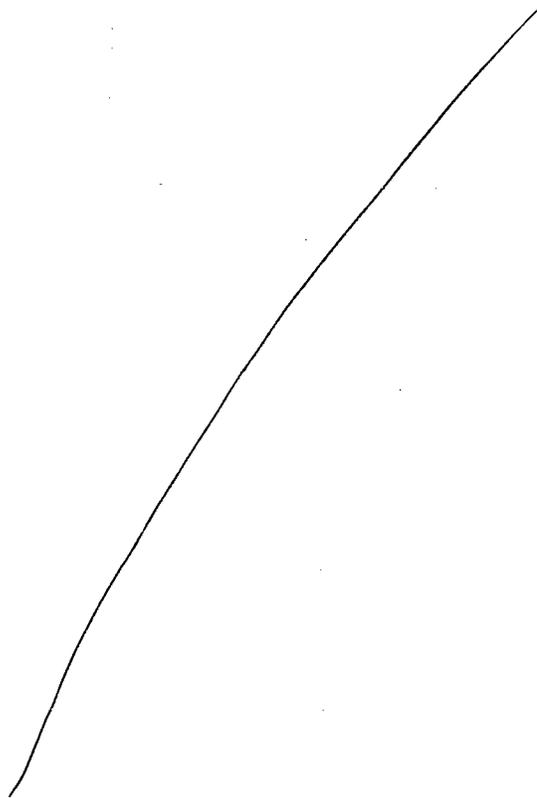
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___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling



STATUS OF OTHER RESPONSES TO APPROVABLE LETTER:

2) Non-critical issues –clearly deficient response

Items that are not deemed critical in terms of their complete resolution prior to approval, but clearly remain unresolved due to a deficient response are listed below. It is recommended that

these be evaluated immediately following the critical issues so that the appropriate request for additional information or revisions can be included in the interim IR letter:

1c, 2d(1)

3) Non-critical issues requiring review

The issues addressed by the following comments are not deemed critical in terms of their complete resolution prior to approval, however, their eventual resolution is important regarding the demonstration and maintenance of product quality. Some of the responses provided include new data requiring review, and protocols for future studies planned in accordance with agreements made with the Agency. In some cases the applicant has *not* strictly complied with the Agency requests but provides justification that will require a detailed review. It is recommended that these be reviewed to the extent possible to generate any necessary requests for inclusion in the interim information request letter:

1b, 1d(5), (9), 1e(1), (3), 2b(1), e, f(1), (2), (6), (7), (9), (10)(a)

4) Non-critical issues with responses considered to be adequate

A preliminary evaluation has lead to the conclusion that the applicant appears to have responded adequately as per the requests for the following comments (and consistent with agreements reached in the 02-MAR-2004 telephone conference), therefore it is not recommended that the evaluation of the responses to these comments be the primary focus during the earlier part of the review when generating an interim information request letter:

1d(1), (2), (4), (6), (7), (8), (10), (11), (12), (13), (14), (15), 1e(2), (4), 1f, g, 2a, b(2), d(2), (5), (6), (7), (9), (11), 2f(3), (4), (5), g

5) Non-critical issues for review in conjunction with a DMF

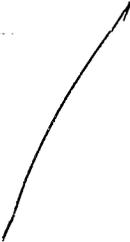
The following comment should be reviewed in conjunction with the response to the 19-DEC-2003, letter forwarded to the holder of DMF —

1a(1), 1h, 2h

CONSULTS REQUESTED:

A consult was forwarded on 13-JUN-2004 to the pharmacology/toxicology (P/T) team regarding the applicant's response to comment 1d(3). The response to comment 2b(1) did include revised limits for the potential volatile impurities





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

CONCLUSION/RECOMMENDATIONS:

- The amendment was considered to be a complete response to the CMC comments included in the 28-NOV-2003, AE letter. However, the actual amendments that have been made to the supporting DMFs will be difficult to review since they are not addressed point-by-point. The PM is currently in contact with the holder of these files to have them submit responses in the typical format, i.e., with specific response to each of the deficiency comments.
- The applicant's response has been examined and the six key issues involve: 1) particle size distribution of micronized drug substance; 2) 3) leachables/extractables controls; 4) lack of specification for drug product foreign particulates; 5) aerodynamic particle size distribution of the drug product; 6) revision of DCU acceptance criteria. Of these six issues it is recommended that the reviewer first focus on the extractables/leachables issue such that a consult for the safety of the levels of these allowed can be assessed by the P/T team.
- No request for inspection via EES is deemed necessary at this time.
- The applicant has provided SAS data files of updated stability data. Once agreement is reached on the DP acceptance criteria (e.g., APSD and DCU), it should be possible to send a consult to biometrics if necessary. Suggested parameters for consideration include and DCU.

Craig M. Bertha, Ph.D.
Chemistry Reviewer

cc:

Orig. NDA 21-457

HFD-570/Div. Files

HFD-570/CBertha 6/24/04

HFD-570/VShah

HFD-570/PPeri

HFD-570/RLostritto

HFD-570/AGreen

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Craig Bertha
7/1/04 05:51:29 AM
CHEMIST

Richard Lostritto
7/2/04 10:29:36 AM
CHEMIST

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ON ORIGINAL**

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

✓ § 552(b)(5) Deliberative Process

 § 552(b)(4) Draft Labeling

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10 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

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3 Page(s) Withheld

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 § 552(b)(5) Deliberative Process

 § 552(b)(4) Draft Labeling



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy, DSI**

FACSIMILE TRANSMITTAL SHEET

DATE: 11/17/2003

To: Peter Starke Akilah Green	From: Amalia Himaya CDER/DSI/HFD-48
HFD-570	CDER
Fax number: 301-827-1271	Fax number: 301-594-1204
Phone number: 301-827-1050 x1263	Phone number: 301-827-7321
Subject: DSI EIR Review of NDA 21-457 Volare (Albuterol Sulfate) Inhalation Aerosol	
Total no. of pages including cover: 24	

Comments:

Hi Peter and Akilah,
Attached is the EIR review for the above subject.
Thanks,
Amalia

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 301-594-0020. Thank you.



ORIGINAL

IVAX Research, Inc.

4400 Biscayne Boulevard

Miami, Florida • 33137

Telephone: 305-575-6000



RECEIVED

JUL 07 2003

FDR/CDER

June 26, 2003

VIA CERTIFIED MAIL

Badrul Chowdhury, M.D.

Director, Division of Pulmonary Drug Products

Food and Drug Administration

Center for Drug Evaluation and Research (HFD-570)

Attention: Document Control Room 10B-03

5600 Fishers Lane

Rockville, MD 20857

N000(C)

NEW CORRESP

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

Re: NDA# 21-457

Volare™ HFA (Albuterol Sulfate, USP) Inhalation Aerosol

Dear Dr. Chowdhury:

Reference is made to our New Drug Application for Albuterol Sulfate HFA Inhalation Aerosol (trade name: Volare™ HFA). The strength is 90 mcg albuterol base through the mouthpiece, and the dosage form for the product is delivery from a metered dose inhaler. Reference is also made to NDA 21-457, submitted on January 30, 2003 and to our Filing Review Letter dated April 15, 2003. IVAX Research, Inc. is hereby providing "Documentation of Notification/Receipt of Notice."

IVAX Research, Inc. has provided appropriate notification to — in accordance with Section 505(b)(3)(A) of the Federal Food, Drug and Cosmetic Act. IVAX Research, Inc. filed an NDA with the intent to engage in commercial manufacture before the expiration of US Patent No. 5,225,183; 5,439,670; 5,605,674; 5,695,743, 5,766,573 and 6,352,684.

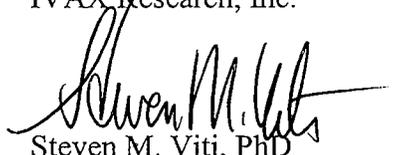
Our notice letter described the factual and legal basis on which we relied in filing a Paragraph IV Certification to each patent and otherwise conformed to the requirements of § 505 (b)(3)(A) and (B) of the Federal Food, Drug and Cosmetic Act. As proof of delivery, we have attached copies of the postal receipt for certified mail, as well the back copy of PS Form 3811.

C O N F I D E N T I A L

IVAX Research, Inc. 4400 Biscayne Boulevard • Miami, Florida • 33137

— has not taken action against IVAX Research, Inc. for infringement of US Patent No. 5,225,183; 5,439,670; 5,605,674; 5,695,743, 5,766,573 and 6,352,684 and the statutory forty five (45) day period for bringing such an action has now expired.

Very truly yours,
IVAX Research, Inc.


Steven M. Viti, PhD
Director, Regulatory Affairs

Certified Mail R.R.R.: Z321 046 201

C O N F I D E N T I A L

IVAX Research, Inc. 4400 Biscayne Boulevard • Miami, Florida • 33137



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
HFD-570 / DPADP

FACSIMILE TRANSMITTAL SHEET

DATE: May 27, 2003

To: Dr. Steve Viti Director, Regulatory Affairs	From: Craig Ostroff, Pharm.D. Project Manager Division of Pulmonary and Allergy Drug Products
Company: IVAX Research	
Fax number: 305-575-6339	Fax number: 301-827-1271
Phone number: 305-575-6336	Phone number: 301-827-5585

Subject: IND 60,549 / , Albuterol HFA MDI 
Official Minutes for November 14, 2001 Meeting

Total no. of pages including cover: 10

Comments: See Attached

Document to be mailed: YES NO

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MEMORANDUM OF MEETING MINUTES

MEETING DATE: November 14, 2001

IND: 60,549 / Albuterol HFA Metered dose inhaler (MDI)

SPONSOR: Ivax Research

TYPE OF MEETING: Pre-NDA (CMC); Face-to-Face; IMTS 7518

ATTENDEES:

Division of Pulmonary & Allergy Drug Products (DPADP, HFD-570)

Craig Bertha, Ph.D.	Chemistry Reviewer
Badrul A. Chowdhury, M.D., Ph.D.	Medical Team Leader
Eric Duffy, Ph.D.	Director, Div New Drug Chemistry II
Collete Jackson	Project Manager
Marianne Mann, M.D.	Deputy Division Director
Craig Ostroff, Pharm.D.	Regulatory Management Officer
Guirag Poochikian, Ph.D.	Chemistry Team Leader
Alan Schroeder, Ph.D.	Chemistry Reviewer

Ivax Research

John Lay	Manager, Regulatory Affairs
Fiona Millar, Ph.D.	Head, Product Development (formulations)
Steve Viti, Ph.D.	Director, Regulatory Affairs
Kai Zhang, Ph.D.	Director, Preformulation

BACKGROUND

IVAX Research (sponsor) submitted a teleconference request with background information that was received on August 17, 2001. The goal of this PNDA meeting was to discuss the status of the overall chemistry development program prior to the submission of the NDA

MEETING DISCUSSION

[NOTE: Comments made by the Division are in a normal font and those of the Sponsor are in italics. Items in brackets, i.e. [], are editorial notes included to aid the reader]

The meeting began with personnel introductions and an overview of the meeting format. The applicant was afforded the opportunity to summarize the points discussed, as they heard them, at the close of the meeting. This summary allows the applicant and FDA the opportunity to clarify any discussion points prior to the meeting's conclusion.

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§ 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
HFD-570 / DPADP

FACSIMILE TRANSMITTAL SHEET

DATE: May 23, 2003

To: Dr. Steve Viti Director, Regulatory Affairs	From: Craig Ostroff, Pharm.D. Project Manager Division of Pulmonary and Allergy Drug Products
Company: IVAX Research	
Fax number: 305-575-6339	Fax number: 301-827-1271
Phone number: 305-575-6336	Phone number: 301-827-5585

Subject: IND 60,549 — Albuterol HFA MDI —
Official Minutes for November 8, 2001 Meeting

Total no. of pages including cover:

Comments: See Attached

Document to be mailed: YES NO

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The meeting began with personnel introductions and an overview of the meeting format. The applicant was afforded the opportunity to summarize the points discussed, as they heard them, at the close of the meeting. The summary allowed the applicant and FDA the opportunity to clarify any discussion points prior to the meeting's conclusion. Attachment 1 contains the clinical slides presented by the Division during the meeting. Attachment 2 contains the toxicology slides presented by the Division.

Toxicology:

The Division commented that the 90-day dog study should use aged product to qualify the maximum expected concentrations of leachables. We also stated to the sponsor that the qualification limits of impurities are as follows: in the drug substance _____, the drug product _____ and the limits for structural alert compounds _____. We reminded the sponsor that they had to assess the leachables for their mutagenic and carcinogenic potential.

The sponsor asked if the 90-day toxicology report could be submitted to the NDA as a non-audited draft report.

The Division said this would be acceptable, as long as the final audited report was submitted as soon as it was available and any differences between the reports were clearly indicated in tabular form and certified to in the cover letter. The Division noted that this is most commonly done for IND submissions, but that it was sometimes allowed for NDA submissions.

Integrated Summary of Safety:

The Division requested a clarification on whether or not a shift table would be generated for each laboratory parameter.

The sponsor responded that a shift table would be generated for each parameter.

Integrated Summary of Efficacy:

The Division outlined that each NDA will require a stand-alone ISE that is more than just the study reports. It should summarize all pivotal studies and provide a full rational explanation of the efficacy of the drug, including a description of the similarities and differences between the MDI, BOI and comparator product. This will impact the proposed labeling of the two test products.

The sponsor indicated that this was their plan and asked whether studies present in more than one study should be pooled.

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§ 552(b)(4) Draft Labeling

CTD/Administrative Issues:

The Division stated that the sponsor's proposed common technical document is acceptable, as outlined in the briefing package.

Module III (CMC) could be submitted up to 60-days early for a CTD, just as with an NDA, if available.

Each discipline review copy must contain Module I and II. Module I may include the EA exemption request. Module I must contain any signed pages. The proposed table of contents is acceptable, at this time.

Additional Comments/Questions:

Ivax asked whether subgroup analysis, such as elderly patients in the 6-week study, could be added.

The Division answered that this could be done in a secondary analysis.

Labeling

The Division stated that the sponsor needed to perform a full review of the current pre-clinical and clinical literature for Albuterol HFA products for inclusion in the appropriate labeling sections

~~_____~~
The division requested the sponsor to update and provide a summary report on albuterol pharmacokinetic data in human from literature articles.

[Post meeting note: The sponsor responded to this request (Clinical pharmacology and Biopharmaceutics), via a fax, in which they asked if they could limit their search to papers on Albuterol HFA products. The Division responded with the following comment to the sponsor: "any new information (other than the study result) from the literature on Albuterol HFA products (e.g., Albuterol by inhalation or non-inhalation route but relevant to your product, new information on drug-drug interaction, etc.) would be appropriate"

Dr. Meyer suggested that the sponsor submit draft labeling soon so that OPDRA can begin review of the proposed proprietary name.

All labeling and PI's should be included in both Word and PDF formats on a disk for the FDA central labeling/PI repository. A list of what should also be included in the attached handout (see page 14 of Attachment 1).

Guidances

The Division reminded the sponsor that there are Clinical and CMC Guidances on the public FDA Web site that the sponsor should consult with before filing the NDA, such as the Points to Consider Guidance. We also reminded the sponsor that the NDA should include an in-vitro comparison of the Reference and Test Products.

[This discussion concluded the meeting]

**APPEARS THIS WAY
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this page is the manifestation of the electronic signature.**

/s/

Craig Ostroff
5/23/03 05:34:20 PM

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 § 552(b)(5) Deliberative Process

 § 552(b)(4) Draft Labeling



FILING REVIEW LETTER

NDA 21-457

Ivax Research, Inc.
4400 Biscayne Boulevard
Miami, FL 33137

Attention: Steven M. Viti, Ph.D.
Director, Regulatory Affairs

Dear Dr. Viti:

Please refer to your January 30, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Volare HFA (albuterol sulfate) Inhalation Aerosol.

We also refer to your submission dated April 1, 2003.

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 April 1, 2003, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing 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.

We request that you submit the following information:

1. Submit a marketing history for your product. We were unable to locate one in your submission.
2. Assure that the Table of Contents (TOC) for all pivotal and supporting studies are complete and include locations for all appendices, tables, etc.
3. The volume jackets were not printed per guidance. Provide a remedy for this issue.
4. The Master TOC is not per guidance and refers to the consecutive volume number instead of the module volume number. Resubmit the Master TOC such that it lists the Module, Module Volume, and Tab divider identifier for each section.
5. The Module TOCs do not have pagination. Resubmit the TOC for each Module such that it lists the Module, Module Volume, and Tab divider identifier, and page numbers for each section.

6. The tab dividers within a Module do not completely conform to the Module TOC, i.e. not every tab has a TOC within it. Each tab that contains more than one document should have a TOC for that section that includes the Module, Module Volume, Tab divider, and page.
7. If a particular section spans multiple volumes, we request that the section TOC be repeated at the front of the volume in order to aid the reviewer.
8. The following specific issues should also be addressed:
 - a. The Case Report Form (CRF) section has no sub-tabs, spans 7 volumes, 8 attachments, and has no location identifiers or pagination. Provide a TOC for this section that includes page numbers and sub-tabs.
 - b. Fill-in the information for the column "Location of Study, Report" for Section 5.2, Tabular Listing of Clinical Studies.
 - c. Resubmit efficacy figures 1 and 2 for Study IX-101-105. These figures were not reproduced clearly in our copy of the submission.
9. Recognizing that this is not a formal electronic submission, modify the electronic portion of the statistical section so that it generally conforms to the file directory system recommended for the clinical section of an electronic NDA submission.
10. Modify the electronic portion of the statistical section to include the locations where all clinical data sections and files may be found in both the paper and electronic formats.
11. Provide the stability data that is currently in the NDA in a database using the SAS transport file format.

We remind you of your commitment dated April 1, 2003, to address these and additional issues with your application in a timely manner.

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.

If you have any questions, call Dr. Craig Ostroff, Regulatory Project Manager, at (301) 827-5585.

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

/s/

Badrul Chowdhury
4/15/03 04:55:32 PM

REQUEST FOR DEFERRAL OF PEDIATRIC STUDIES

NDA Number: 21-457

Sponsor: IVAX Research, Inc.

Product name:

Volare™ HFA (Albuterol Sulfate, USP) Inhalation Aerosol

Indication:

For the treatment or prevention of bronchospasm with reversible obstructive airway disease

Age Groups Included in Deferral Request:

Children between the ages of 4 to 11 years old.

Reason for not including Entire Pediatric Population:

The use of MDIs is not practical in children of younger ages. Several nebulized formulations are available for prescription in the USA, which have indication for use in children <4 years old.

Reason For Deferring the Studies:

Our clinical plan calls for conducting a pediatric program once the adult/adolescent program has been completed and the NDA submitted to the Agency for review. We will initiate a pediatric clinical program

C O N F I D E N T I A L

IVAX Research, Inc. 4400 Biscayne Boulevard • Miami, Florida • 33137



Steven M. Viti, Ph.D.
Director, Regulatory Affairs

1/29/03
Date

1.2.5 User Fee

A copy of the cover sheet of the User Fee application is attached. This was submitted on December 5, 2002. Also included are copies of the check and Federal Express tracking form.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	Form Approved: OMB No. 0910-3297 Expiration Date: February 29, 2004. <h2 style="text-align: center;">USER FEE COVER SHEET</h2>						
<p>See Instructions on Reverse Side Before Completing This Form</p> <p>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/pdula/default.htm</p>							
1. APPLICANT'S NAME AND ADDRESS IVAX Research, Inc. 4400 Biscayne Boulevard* Miami, FL 33137	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER NDA 21-457						
2. TELEPHONE NUMBER (Include Area Code) (305) 575-6336	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: _____ (APPLICATION NO. CONTAINING THE DATA).						
3. PRODUCT NAME Volare™ HFA (Albuterol Sulfate, USP) Inhalation Aerosol	6. USER FEE I.D. NUMBER 4464						
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION. <table style="width:100%; margin-top: 10px;"> <tr> <td style="width:50%; vertical-align: top;"> <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) </td> <td style="width:50%; vertical-align: top;"> <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.) </td> </tr> <tr> <td style="vertical-align: top;"> <input type="checkbox"/> 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.) </td> <td style="vertical-align: top;"> <input type="checkbox"/> 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.) </td> </tr> <tr> <td colspan="2" style="vertical-align: top; text-align: center;"> <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory) </td> </tr> </table>		<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)	<input type="checkbox"/> 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.)	<input type="checkbox"/> 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.)	<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)	
<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)						
<input type="checkbox"/> 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.)	<input type="checkbox"/> 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.)						
<input type="checkbox"/> 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? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO (See Item 8, reverse side if answered YES)							
<p>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:</p> <table style="width:100%; margin-top: 10px;"> <tr> <td style="width:33%;"> Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448 </td> <td style="width:33%; text-align: center; vertical-align: middle;"> and </td> <td style="width:33%;"> Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852 </td> </tr> </table> <p style="text-align: right; margin-top: 10px;">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.</p>		Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	and	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852			
Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	and	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852					
SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE Director, Regulatory Affairs						
DATE December 5, 2002							

1.2.6 Financial Certification/Information

Completed, signed Forms FDA 3454 – “Certification: Financial Interests and Arrangements of Clinical Investigators,” and FDA 3455 “Disclosure: Financial Interests and Arrangements of Clinical Investigators” are provided on the following pages.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Form Approved: OMB No. 0916-0596
Expiration Date: June 30, 2002

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

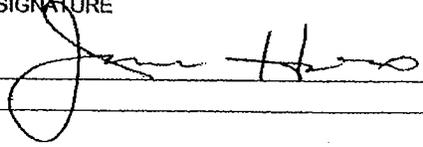
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the 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	

- (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 Jane Hsiao		TITLE Vice President	
FIRM / ORGANIZATION IVAX Research, Inc.			
SIGNATURE 		DATE Dec. 6, 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

7 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

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Telephone: 305-575-6000



January 30, 2002

Badrul Chowdhury, M.D.
Acting Director, Division of Pulmonary Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-570)
Attention: Document Control Room 10B-45
5600 Fishers Lane
Rockville, MD 20857

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JAN 31 2003

CDR/CDER

Re: NDA 21-457

Volare™ HFA (Albuterol Sulfate, USP) Inhalation Aerosol
User Fee ID No. 4464

RECEIVED

FEB 04 2003

FDR/CDER

Dear Dr. Chowdhury:

Under the provisions of 21 CFR 314.54, IVAX Research, Inc. is submitting its New Drug Application for Volare™ HFA (Albuterol Sulfate, USP) Inhalation Aerosol, a CFC-free aerosol formulation of albuterol sulfate for use in the treatment or prevention of bronchospasm with reversible obstructive airway disease

This product utilizes a hydrofluoroalkane (HFA) propellant, 1,1,1,2-tetrafluoroethane (HFA-134a), that should have no or minimal effect on ozone depletion. As discussed in our pre-NDA meetings of November 8 and 14, 2001, Proventil® HFA was used as the comparator in our clinical studies; and this submission therefore is being presented as a 505(b)(2) application.

Volare™ has been developed and is to be manufactured by our affiliated company, IVAX Pharmaceuticals, Inc., located in Waterford, Ireland. IVAX Pharmaceuticals, Waterford and IVAX Research, Miami are wholly-owned subsidiaries of the IVAX Corporation. A field copy of the CMC portion of this application has been sent to Irma Rivera, Program Specialist in Rockville, MD.

This paper application has been formatted in accordance with the Common Technical Document format, as described in the August 2001 Guidance for Industry: *Submitting Marketing Applications According to the ICH-CTD Format-General Considerations* and *M4: Organization of the CTD*.

Module 1 Consists of 1 volume, and contains the **Administrative Information and Prescribing Information**.

Module 2 Consists of 2 volumes, and contains the **Common Technical Document Summaries**.

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IVAX Research, Inc. 4400 Biscayne Boulevard • Miami, Florida • 33137