CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-730

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

84 Waterford Drive
Marlborough, MA 01752

Phone: (508) 481-6700
Fax: (508) 357-7491

FAX COVER SHEET

TO: Akilah Green Senior Regulatory Manager	FROM: Jerry Klimek
Company: FDA, CDER, ODEII Div. of Pulmonary Drug Prod.	Title: Senior Director Regulatory Affairs
Phone: (301) 827-1050	Phone: (508) 357-7743
Fax: (301) 827-1271	Fax: (508) 357-7491

Date: March 3, 2005
Pages: 8 (including this cover sheet)
Re: **NDA 21-730 Xopenex HFA™ (levalbuterol tartrate) Inhalation Aerosol Response to FDA Request for Information**

MESSAGE

Dear Ms. Green;

Attached is a copy of the requested paragraph IV certifications for our Xopenex HFA™ (levalbuterol tartrate) Inhalation Aerosol NDA 21-730. This information will be formally submitted to the electronic NDA as soon as possible.

Sincerely,

Jerry Klimek
Senior Director, Regulatory Affairs

SEPRACOR

March 9, 2005

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

Re: **NDA 21-730**
Xopenex HFA™ (levalbuterol tartrate) Inhalation Aerosol
Response to FDA Request for Information of March 8, 2005:
Paragraph IV Certifications

Dear Dr. Chowdhury:

Please reference Sepracor Inc.'s pending NDA 21-730 for Xopenex HFA™ (levalbuterol tartrate) Inhalation Aerosol submitted on May 11, 2004. Please also reference the teleconference on March 8, 2005, between the FDA (Akilah Green, Regulatory Project Manager; Kim Colangelo, Consumer Safety Officer; and Wayne Mitchell, Regulatory Counsel) and Sepracor (Jerry Klimek, Senior Director, Regulatory Affairs; Doug Reedich, Senior Vice President, Legal Affairs; and Stewart H. Mueller, Senior Vice President, Regulatory Affairs and Quality Assurance) regarding Paragraph IV Certifications.

The purpose of this submission is to provide the requested Paragraph IV Certifications for our Xopenex HFA™ (levalbuterol tartrate) Inhalation Aerosol, NDA 21-730.

If further information is needed, please contact me by telephone at (508)-357-7743 or by fax at (508) 357-7491.

Sincerely,

Jerry Klimek
Senior Director, Regulatory Affairs

Sepracor Inc., 84 Waterford Drive, Marlborough, MA 01752 Tel: (508) 481-6700 Fax: (508) 481-7683

SEPRACOR

March 9, 2005

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA NUMBER 21-730, SEPRACOR INC.

PARAGRAPH (iv) CERTIFICATION
United States Patent No. 5,766,573

Dear Sir/Madam:

This letter is submitted under 21 USC 505(b)(2) and 21 CFR 314.50(i) in connection with Sepracor Inc.'s New Drug Application No. 21-730 for XOPENEX HFA (levalbuterol tartrate) inhalation aerosol.

Sepracor Inc. has been granted a patent license for XOPENEX HFA inhalation aerosol under United States Patent No. 5,766,573 by the owner of said patent. Accordingly, Sepracor Inc. hereby certifies that United States Patent No. 5,766,573 will not be infringed by the manufacture, use, or sale of XOPENEX HFA (levalbuterol tartrate) inhalation aerosol for which this New Drug Application 21-730 is submitted.

Sepracor Inc. will give the notice required by 21 USC 505(b)(3)(B) and 21CFR 314.52(a) to each owner of the patent or the representative of such owner designated to receive such notice and to the holder of the approved application under 21 USC 505(b) for the drug which is claimed by the patent or a use of which is claimed by the patent or the representative of such holder designated to receive such notice.

Very truly yours,

Douglas E. Reedich
Sr. Vice President Legal Affairs

Sepracor Inc., 84 Waterford Drive, Marlborough, MA 01752 Tel: (508) 481-6700 Fax: (508) 481-7683

SEPRACOR

March 9, 2005

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA NUMBER 21-730, SEPRACOR INC.

PARAGRAPH (iv) CERTIFICATION
United States Patent No. 6,352,684

Dear Sir/Madam:

This letter is submitted under 21 USC 505(b)(2) and 21 CFR 314.50(i) in connection with Sepracor Inc.'s New Drug Application No. 21-730 for XOPENEX HFA (levalbuterol tartrate) inhalation aerosol.

Sepracor Inc. has been granted a patent license for XOPENEX HFA inhalation aerosol under United States Patent No. 6,352,684 by the owner of said patent. Accordingly, Sepracor Inc. hereby certifies that United States Patent No. 6,352,684 will not be infringed by the manufacture, use, or sale of XOPENEX HFA (levalbuterol tartrate) inhalation aerosol for which this New Drug Application 21-730 is submitted.

Sepracor Inc. will give the notice required by 21 USC 505(b)(3)(B) and 21CFR 314.52(a) to each owner of the patent or the representative of such owner designated to receive such notice and to the holder of the approved application under 21 USC 505(b) for the drug which is claimed by the patent or a use of which is claimed by the patent or the representative of such holder designated to receive such notice.

Very truly yours,

Douglas E. Reedich
Sr. Vice President Legal Affairs

SEPRACOR

March 9, 2005

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA NUMBER 21-730, SEPRACOR INC.

PARAGRAPH (iv) CERTIFICATION
United States Patent No. 5,695,743

Dear Sir/Madam:

This letter is submitted under 21 USC 505(b)(2) and 21 CFR 314.50(i) in connection with Sepracor Inc.'s New Drug Application No. 21-730 for XOPENEX HFA (levalbuterol tartrate) inhalation aerosol.

Sepracor Inc. has been granted a patent license for XOPENEX HFA inhalation aerosol under United States Patent No. 5,695,743 by the owner of said patent. Accordingly, Sepracor Inc. hereby certifies that United States Patent No. 5,695,743 will not be infringed by the manufacture, use, or sale of XOPENEX HFA (levalbuterol tartrate) inhalation aerosol for which this New Drug Application 21-730 is submitted.

Sepracor Inc. will give the notice required by 21 USC 505(b)(3)(B) and 21CFR 314.52(a) to each owner of the patent or the representative of such owner designated to receive such notice and to the holder of the approved application under 21 USC 505(b) for the drug which is claimed by the patent or a use of which is claimed by the patent or the representative of such holder designated to receive such notice.

Very truly yours,

Douglas E. Reedich
Sr. Vice President Legal Affairs

Sepracor Inc., 84 Waterford Drive, Marlborough, MA 01752 Tel: (508) 481-6700 Fax: (508) 481-7683

SEPRACOR

March 9, 2005

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA NUMBER 21-730, SEPRACOR INC.

PARAGRAPH (iv) CERTIFICATION
United States Patent No. 5,605,674

Dear Sir/Madam:

This letter is submitted under 21 USC 505(b)(2) and 21 CFR 314.50(i) in connection with Sepracor Inc.'s New Drug Application No. 21-730 for XOPENEX HFA (levalbuterol tartrate) inhalation aerosol.

Sepracor Inc. has been granted a patent license for XOPENEX HFA inhalation aerosol under United States Patent No. 5,605,674 by the owner of said patent. Accordingly, Sepracor Inc. hereby certifies that United States Patent No. 5,605,674 will not be infringed by the manufacture, use, or sale of XOPENEX HFA (levalbuterol tartrate) inhalation aerosol for which this New Drug Application 21-730 is submitted.

Sepracor Inc. will give the notice required by 21 USC 505(b)(3)(B) and 21CFR 314.52(a) to each owner of the patent or the representative of such owner designated to receive such notice and to the holder of the approved application under 21 USC 505(b) for the drug which is claimed by the patent or a use of which is claimed by the patent or the representative of such holder designated to receive such notice.

Very truly yours,

Douglas E. Reedich
Sr. Vice President Legal Affairs

SEPRACOR

March 9, 2005

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA NUMBER 21-730, SEPRACOR INC.

PARAGRAPH (iv) CERTIFICATION
United States Patent No. 5,439,670

Dear Sir/Madam:

This letter is submitted under 21 USC 505(b)(2) and 21 CFR 314.50(i) in connection with Sepracor Inc.'s New Drug Application No. 21-730 for XOPENEX HFA (levalbuterol tartrate) inhalation aerosol.

Sepracor Inc. has been granted a patent license for XOPENEX HFA inhalation aerosol under United States Patent No. 5,439,670 by the owner of said patent. Accordingly, Sepracor Inc. hereby certifies that United States Patent No. 5,439,670 will not be infringed by the manufacture, use, or sale of XOPENEX HFA (levalbuterol tartrate) inhalation aerosol for which this New Drug Application 21-730 is submitted.

Sepracor Inc. will give the notice required by 21 USC 505 (b)(3)(B) and 21CFR 314.52(a) to each owner of the patent or the representative of such owner designated to receive such notice and to the holder of the approved application under 21 USC 505(b) for the drug which is claimed by the patent or a use of which is claimed by the patent or the representative of such holder designated to receive such notice.

Very truly yours,

Douglas E. Reedich
Sr. Vice President Legal Affairs

Sepracor Inc., 84 Waterford Drive, Marlborough, MA 01752 Tel: (508) 481-6700 Fax: (508) 481-7683

SEPRACOR

March 9, 2005

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA NUMBER 21-730, SEPRACOR INC.

PARAGRAPH (iv) CERTIFICATION
United States Patent No. 5,225,183

Dear Sir/Madam:

This letter is submitted under 21 USC 505(b)(2) and 21 CFR 314.50(i) in connection with Sepracor Inc.'s New Drug Application No. 21-730 for XOPENEX HFA (levalbuterol tartrate) inhalation aerosol.

Sepracor Inc. has been granted a patent license for XOPENEX HFA inhalation aerosol under United States Patent No. 5,225,183 by the owner of said patent. Accordingly, Sepracor Inc. hereby certifies that United States Patent No. 5,225,183 will not be infringed by the manufacture, use, or sale of XOPENEX HFA (levalbuterol tartrate) inhalation aerosol for which this New Drug Application 21-730 is submitted.

Sepracor Inc. will give the notice required by 21 USC 505 (b)(3)(B) and 21CFR 314.52(a) to each owner of the patent or the representative of such owner designated to receive such notice and to the holder of the approved application under 21 USC 505(b) for the drug which is claimed by the patent or a use of which is claimed by the patent or the representative of such holder designated to receive such notice.

Very truly yours,

Douglas E. Reedich
Sr. Vice President Legal Affairs

Patent Information on Any Patent That Claims the Drug

This section provides patent information on the following patents covering Sepracor's NDA 21-730 for levalbuterol tartrate HFA:

- U.S. Patent No. 5,362,755
- U.S. Patent No. 5,547,994
- U.S. Patent No. 5,760,090
- U.S. Patent No. 5,844,002
- U.S. Patent No. 6,083,993
- U.S. Patent No. 5,836,299
- U.S. Patent No. 5,605,674
- U.S. Patent No. 5,225,183
- U.S. Patent No. 5,695,743
- U.S. Patent No. 5,439,670
- U.S. Patent No. 6,352,684

A Patent Certification with Respect to Any Patent That Claims the Drug

This section provides information related to patent certification and claimed exclusivity for NDA 21-730.

April 5, 2004

Central Document Room
Center for Drug Evaluation Research
FOOD AND DRUG ADMINISTRATION
12229 Wilkins Avenue
Rockville, MD 20852

RE: **NDA NUMBER 21-730, SEPRACOR INC.**
REQUEST FOR NEW DRUG PRODUCT EXCLUSIVITY

Dear Sir/Madam:

This letter is submitted under 21 USC §355(b)(1) in connection with Sepracor's New Drug Application No. 21-730 for levalbuterol tartrate HFA.

The active ingredient (or salt or ester thereof) of levalbuterol tartrate HFA has been previously approved by FDA in another application submitted under 21 USC 355 (b). Accordingly, Sepracor respectfully requests that, upon approval of NDA Number 21-730, FDA grant a three (3) year period of exclusivity under 21 USC 355(c)(3)(D)(iii), and 21 CFR 314.108(b)(4).

VERY TRULY YOURS,

Douglas E. Reedich
Sr. Vice President, Legal Affairs
& Chief Patent Counsel

April 5, 2004

Central Document Room
Center for Drug Evaluation Research
FOOD AND DRUG ADMINISTRATION
12229 Wilkins Avenue
Rockville, MD 20852

RE: **NDA NUMBER 21-730, SEPRACOR INC.**
PATENT CERTIFICATION

Dear Sir/Madam:

This letter is submitted under 21 USC §355(b)(1) in connection with Sepracor's New Drug Application No. 21-730 for levalbuterol tartrate HFA.

In the opinion and to the best knowledge of Sepracor, there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted, or that claim a use of such drug or drugs.

VERY TRULY YOURS,

Douglas E Reedich

DOUGLAS E. REEDICH
Sr. Vice President, Legal Affairs
& Chief Patent Counsel

EXCLUSIVITY SUMMARY FOR NDA # **21-730** SUPPL #_____

Trade Name **Xopenex HFA Inhalation Aerosol** Generic Name _____

Applicant Name **Sepracor** HFD # **570**

Approval Date If Known **March 11, 2005**

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)(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 /**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:

_____

_____

d) Did the applicant request exclusivity?

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

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

3 Years

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

YES /__/ NO /**X**/

If the answer to the above question is 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 /**X**/

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 /**X**/ NO /___/

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

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 /___/ NO /X/

(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 /___/

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:

051-353 051-355 051-354

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 to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1-3 YES /___/ NO /**X**/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1-3 YES /___/ NO /**X**/

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"):

051-353 051-355 051-354

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 # 62,906 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**/

If yes, explain: _____

_____

Signature: **Akilah Green** Date
Title: **Regulatory Project Manager**

Signature:
Office/Division Director: **Badrul A. Chowdhury, M.D., Ph.D.**
Date:

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Badrul Chowdhury
3/11/05 02:32:47 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # :21-730 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: May 12, 2004 PDUFA Goal Date: March 12, 2005

HFD -570 Trade and generic names/dosage form: Xopenex HFA Inhalation Aerosol

Applicant: Sepracor Therapeutic Class: Standard

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

√Yes. Please proceed to the next section.

No. PREA does not apply. Skip to signature block.

** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.*

Indication(s) previously approved (please complete this section for supplements only):
(Each indication covered by this application must have pediatric studies: Completed, Deferred, and/or Waived.)

Number of indications for this application(s): 1

Indication #1: treatment or prevention of bronchospasm in adults, adolescents, and children 4 years of age and older with reversible obstructive airway disease.

Is this an orphan indication?

- ☐ **Yes. PREA does not apply. Skip to signature block.**

√No. Please proceed to the next question.

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.

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: Akilah Green, Regulatory Project Manager

{See appended electronic signature page}

Regulatory Project Manager

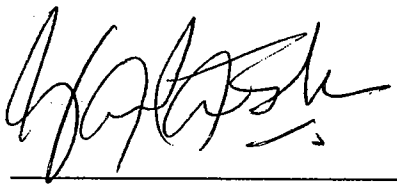
cc: NDA 21-730
HFD-960/ Rosemary Addy or Grace Carmouze

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

(revised 2-28-2005)

Debarment Certification

Sepracor 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 New Drug Application for Xopenex HFA™ (levalbuterol tartrate HFA) Inhalation Aerosol.



Gautam Shah, Ph.D.
Senior Director, Regulatory Affairs

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-730	Efficacy Supplement Type SE-	Supplement Number	
Drug: **Xopenex HFA (levalbuterol tartrate) Inhalation Aerosol**		Applicant: **Sepracor**	
RPM: **Akilah Green**		HFD- **570**	Phone # **827-5585**

Application Type: ( ) 505(b)(1) **(X)** 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.) **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.** ( ) Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): NDA 19-243/ Proventil Inhalation Aerosol/ Schering Corporation

❖ Application Classifications:	
• Review priority	**(X)** Standard ( ) Priority
• Chem class (NDAs only)	
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	**March 12, 2005**
❖ Special programs (indicate all that apply)	**(X)** None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	**(X)** Paid UF ID number **#4738**
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes **(X)** No

• This application is on the AIP	( ) Yes (X) 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 & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) (X) Verified 21 CFR 314.50(i)(1) (X) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	( ) N/A (no paragraph IV certification) (X) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).* (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *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 (3).* (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	(X) Yes ( ) No (X) Yes ( ) No ( ) 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**," 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? (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.*	( ) Yes ( ) No
❖ Exclusivity (approvals only)	
• 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.)	**No**
• 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.*	( ) Yes, Application #_____ **(X)** No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	**June 22, 2005, March 7, 2005**

General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release ( ) Talk Paper ( ) 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)	**February 25, 2005, March 9, 2005**
• Most recent applicant-proposed labeling	**February 4, March 3, 2005**
• Original applicant-proposed labeling	**May 11, 2004**
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	**February 14, 2005, November 17, 2004**
• 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)	**March 4, 2005**
• Applicant proposed	**May 11, 2004**
• Reviews	**November 17, 2004**
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	**January 5, March 11, 2005**
• Documentation of discussions and/or agreements relating to post-marketing commitments	**February 25, January 3, 2005**
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	**May 19, August 10, September 28, December 22, 2004, January 7, February 8, 15, 22, 25, March 4, 9, 2005.**
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	**October 29, 2003**
• Pre-NDA meeting (indicate date)	**September 30, 2003, and January 5, 2004**
• 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 reports (if applicable)	

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	**March 11, 2005**
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	**February 25, 2005, July 1, 2004**
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	**February 25, 2005**
❖ 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)	**March 11, 2005**
❖ Demographic Worksheet *(NME approvals only)*	**N/A**
❖ Statistical review(s) *(indicate date for each review)*	**February 18, 2005**
❖ Biopharmaceutical review(s) *(indicate date for each review)*	**June 29, 2004, March 7, 2005**
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	**February 22, 2005**
• Bioequivalence studies	
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	**January 3, March 9, 2005, June 23, 2004**
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	**January 3, 2005**
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	**March 4, 2005**
❖ Facilities inspection (provide EER report)	Date completed: **August 25, 2004** **(X)** Acceptable **( )** Withhold recommendation
❖ Methods validation	**( )** Completed **(X)** Requested **( )** Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	**February 23, 2005**
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	
❖ CAC/ECAC report	

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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

FACSIMILE TRANSMITTAL SHEET

Date: March 11, 2005

To: Jerry Klimek **Senior Director, Regulatory Affairs**	**From:** Akilah Green, RN Regulatory Project Manager
Company: Sepracor Inc.	Division of Pulmonary and Allergy Drug Products
Fax number: 508-357-7491	**Fax number:** 301-827-1271
Phone number: 508-357-7743	**Phone number:** 301-827-5585

Subject: NDA 21-730 Approval Letter

Total no. of pages including cover: 26

Comments:

Document to be mailed: X YES NO

14

4 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: March 9, 2005

To: Jerry Klimek **Senior Director, Regulatory Affairs**	**From:** Akilah Green, RN Regulatory Project Manager
Company: Sepracor Inc.	Division of Pulmonary and Allergy Drug Products
Fax number: 508-357-7491	**Fax number:** 301-827-1271
Phone number: 508-357-7743	**Phone number:** 301-827-5585

Subject: NDA 21-730, Labeling comments #3

Total no. of pages including cover:

Comments:

Document to be mailed: YES XNO

We have some additional comments regarding your proposed Package Insert, for NDA 21-730. Submit revised draft labeling incorporating the revisions listed below.

1. Line 224 - Change levalbuterol to XOPENEX HFA

2. Line 268 - Change levalbuterol to XOPENEX HFA

3. Title of Table 2 - insert a space between the ≥ sign and the number 12

4. In the last paragraph of the Teratogenic Effects section, insert a sentence regarding congenital anomalies reported in postmarketing experience with levalbuterol inhalation solution.

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

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
3/9/05 03:44:27 PM
CSO

84 Waterford Drive
Marlborough, MA 01752

Phone: (508) 481-6700
Fax: (508) 357-7491

FAX COVER SHEET

TO: Akilah Green Senior Regulatory Manager	FROM: Jerry Klimek
Company: FDA, CDER, ODEII Div. of Pulmonary Drug Prod.	Title: Senior Director Regulatory Affairs
Phone: (301) 827-1050	Phone: (508) 357-7743
Fax: (301) 827-1271	Fax: (508) 357-7491

Date: March 9, 2005
Pages: 3 (including this cover sheet)
Re: **NDA 21-730: Xopenex HFA™ (levalbuterol tartrate) Inhalation Aerosol**
Response to FDA Request for Information of March 8, 2005:
3M Pharmaceuticals Consent Letter

MESSAGE

Dear Ms. Green:

Attached is a copy of the requested consent letter from 3M Pharmaceuticals in regard to the license granted by 3M to Sepracor for Xopenex HFA™ (levalbuterol tartrate) Inhalation Aerosol, NDA 21-730. This information will be formally submitted to the electronic NDA as soon as possible.

Sincerely,

Jerry Klimek
Senior Director, Regulatory Affairs

SEPRACOR

March 9, 2005

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

Re: **NDA 21-730**
Xopenex HFA™ (levalbuterol tartrate) Inhalation Aerosol
Response to FDA Request for Information of March 8, 2005:
3M Pharmaceuticals Consent Letter

Dear Dr. Chowdhury:

Please reference Sepracor Inc.'s pending NDA 21-730 for Xopenex HFA™ (levalbuterol tartrate) Inhalation Aerosol submitted on May 11, 2004. Please also reference the teleconference on March 8, 2005, between the FDA (Akilah Green, Regulatory Project Manager; Kim Colangelo, Consumer Safety Officer; and Wayne Mitchell, Regulatory Counsel) and Sepracor (Jerry Klimek, Senior Director, Regulatory Affairs; Doug Reedich, Senior Vice President, Legal Affairs; and Stewart H. Mueller, Senior Vice President, Regulatory Affairs and Quality Assurance) regarding consent from 3M Pharmaceuticals.

The purpose of this submission is to provide the requested consent letter from 3M Pharmaceuticals in regard to the license granted by 3M to Sepracor for Xopenex HFA™ (levalbuterol tartrate) Inhalation Aerosol, NDA 21-730.

If further information is needed, please contact me by telephone at (508)-357-7743 or by fax at (508) 357-7491.

Sincerely,

Jerry Klimek
Senior Director, Regulatory Affairs

Ted K. Ringsred
Intellectual Property Counsel

Office of Intellectual
Property Counsel

3M Innovative Properties Company
3M Center
PO Box 33427
St. Paul, MN 55133-3427 USA
651 736 5839
651 736 3833 Fax
tringsred@mmm.com

3M

March 9, 2005

Douglas E. Reedich, Esq.
Sr. Vice President Legal Affairs
Sepracor Inc.
84 Waterford Drive
Marlborough, MA 01752

Re: NDA 21-730 paragraph (iv) certification to 3M

Dear Mr. Reedich:

We understand that Sepracor Inc. has submitted New Drug Application No. 21-730 under 21 USC 505(b)(2) for XOPENEX HFA (levalbuterol tartrate) Inhalation Aerosol to obtain approval to engage in the commercial manufacture, use, or sale of XOPENEX HFA (levalbuterol tartrate HFA) metered-dose inhaler before the expiration dates of United States Patent Nos. 5,225,183, 5,695,743, 5,439,670, 5,605,674, 5,766,573, and 6,352,684, all owned by Riker Laboratories, Inc. (a/k/a 3M Pharmaceuticals), a wholly-owned subsidiary of 3M Company ("3M"). We are in receipt of Sepracor's notice of certification under 21 USC 505(b)(2)(A) (iv) that these patents will not be infringed by the manufacture, use, or sale of XOPENEX HFA (levalbuterol tartrate HFA) metered-dose inhaler due to a license from 3M. This letter acknowledges that 3M has granted a license under these patents to Sepracor for XOPENEX HFA and that 3M consents to an immediate effective date upon approval of Sepracor's application under 21 USC 505(b)(2).

Sincerely,

Ted Ringsred

Ted K. Ringsred

MEMORANDUM

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

DATE: March 8, 2005

TO: NDA 21-730

FROM: Akilah Green
Regulatory Project Manager

SUBJECT: **Patent Certification**

A teleconference was held between members of Sepracor (Jerry Klimek, Stewart Muller, and Douglas Reedich) and the Food and Drug Administration (Akilah Green, Kim Colangelo, and Wayne Mitchell) to discuss patent certification.

Sepracor was informed that because their new drug application (NDA) 21-730 is a 505(b)(2) application, they are required to provide patent certification. When Sepracor submitted their NDA, they provided a list of patents, a right of reference to the clinical data from 3M for Proventil HFA, and a patent certification statement. Sepracor did not identify the type of patent they were certifying to (Paragraph III or Paragraph IV).

Sepracor noted that they have a licensing agreement with 3M. However, they did not provide a copy of the licensing agreement with the NDA. Sepracor was told that they need to file paragraph IV (no infringement) for the Proventil HFA patents, and they should also submit proof of the licensing agreement with 3M. In addition, they need a letter from 3M stating that they are okay with the immediate marketing of Xopenex HFA Inhalation Aerosol and will not sue Sepracor for patent infringement for the paragraph IV certification. Otherwise, we will need to wait 45 days to allow 3M to sue them (required by law).

Sepracor verbalized an understanding of the patent information, certification, and requirements. The Agency also pointed out the regulations 21 CFR 314.50 (i) for Sepracor to refer to. Sepracor stated that they will submit the requested information to the Division.

Akilah Green
Regulatory Project Manager

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
3/9/05 10:07:11 AM
CSO

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

FACSIMILE TRANSMITTAL SHEET

Date: March 4, 2005

To: Jerry Klimek **Senior Director, Regulatory Affairs**	**From:** Akilah Green, RN Regulatory Project Manager
Company: Sepracor Inc.	Division of Pulmonary and Allergy Drug Products
Fax number: 508-357-7491	**Fax number:** 301-827-1271
Phone number: 508-357-7743	**Phone number:** 301-827-5585

Subject: NDA 21-730 Comments on the carton and container

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES XNO

NDA 21-730
Xopenex HFA

Your submission dated May 11, 2004, to NDA# 21-730, is currently under review and we have the following comments:

1. Make sure the font of the established name so that it is at least ½ the size of the proprietary name. See 21 CFR 201.10(g)(2).

2. The ~ lettering on the ~ background is difficult to read and may lead to errors. Use a color combination that provides sufficient contrast and greater readability.

3. Delete the graphic ~ as it is distracting and interferes with the readability of the name.

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

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
3/4/05 02:45:07 PM
CSO

84 Waterford Drive
Marlborough, MA 01752

Phone: (508) 481-6700
Fax: (508) 357-7491

FAX COVER SHEET

TO: Akilah Green Senior Regulatory Manager	FROM: Jerry Klimek
Company: FDA, CDER, ODEII Div. of Pulmonary Drug Prod.	Title: Senior Director Regulatory Affairs
Phone: (301) 827-1050	Phone: (508) 357-7743
Fax: (301) 827-1271	Fax: (508) 357-7491

Date: March 4, 2005
Pages: 3 (including this cover sheet)
Re: **NDA 21-730 Xopenex HFA™ (levalbuterol tartrate) Inhalation Aerosol**

MESSAGE

Dear Akilah;

In reference to your request, attached please find a copy of the 3M Letter of Cross-Reference located on pages 10067-10068 of the Integrated Summary of Safety, in the original Xopenex HFA Inhalation Aerosol NDA No. 21-730. The electronic location of this letter is as follows:

clinstat\iss\iss.pdf Item 22 - 3M Letter of Cross-Reference

Thank you,

Jerry Klimek
Senior Director, Regulatory Affairs

3M Drug Delivery Systems Division
3M Pharmaceuticals Division

3M Center, Building 0270-03-A-08
St. Paul, MN 55144-1000

3M March 25, 2004

Badrul Chowdhury, MD
Division Director
Division of Pulmonary and Allergy Drug Products (HFD-570)
Center for Drug Evaluation and Research
Food and Drug Administration
Room 10B-45
5600 Fishers Lane
Rockville, MD 20857

Subject: **NDA 20-503: Proventil® HFA (albuterol sulfate) Inhalation Aerosol**

Renewal of Authorization to Reference Select Sections of NDA 20-503 on Behalf of Sepracor Inc.

Attn: **Akilah Green**

Dear Dr. Chowdhury:

3M Pharmaceuticals, sponsor and owner of NDA 20-503 (Proventil® HFA (albuterol sulfate) Inhalation Aerosol), authorizes FDA to access the noted sections of NDA 20-503 for purposes of:

1. assessing the safety of a new drug product, levalbuterol tartrate HFA MDI, with respect to ongoing and future investigational activities being conducted by Sepracor Inc. under IND 62,906, and the adequacy of such development program to support NDA 21-730, Xopenex HFA™ (levalbuterol tartrate HFA) Inhalation Aerosol, and

2. assessing the safety of this new drug product during review of NDA 21-730.

This reference will serve to incorporate data that substantiate the "long term" safety of an albuterol sulfate HFA MDI, representing a total of 393 patients exposed to the drug product for 12 months. It also incorporates additional safety data summarized in the Integrated Summary of Safety (ISS) for NDA 20-503.

Authorization to Reference NDA 20-503
March 25, 2004
Page 2 of 2

This authorization extends to the following sections of NDA 20-503:

- Section 3.2 Rationale, Use and Benefits (Volume 5.1, Pages 67 - 69),
- Section 3.5 Non-clinical Pharmacology and Toxicology Summary (Volume 5.1, Pages 80 - 133),
- Section 3.7 Clinical Summary (Volume 5.1, Pages 166 - 330),
- Section 7 Non-clinical Pharmacology and Toxicology (Volume 5.1, Pages 414 - End of Vol. 5.1),
- Section 10 Clinical Data (Volumes 5.6 - 5.93, Page 285),
- Section 11 Statistical (Volumes 5.93 - 5.167),
- Section 12 Case Report Tabulations (Volume 5.168, Pages 1 - 21),
- Section 13 Case Report Forms (Volume 5.168, Pages 22 - 29).

Please don't hesitate to contact me (651 736-5015) if you have any questions about this reference.

Respectfully,

D. M. Markoe

David M. Markoe, Jr.
Senior Regulatory Specialist
3M Drug Delivery Systems Division

c: Stewart Mueller
Sepracor
84 Waterford Drive
Marlborough, MA 01752

NDA 21-730

Regulatory Project Management Labeling Review

Sepracor submitted draft labeling for their new drug application for NDA 21-730, Xopenex HFA Inhalation Aerosol, on May 11, 2004. The labeling provided for the use of Xopenex HFA Inhalation Aerosol for treatment or prevention of bronchospasm in adults, adolescents, and children, 4 years of age and older with reversible obstructive airway.

Labeling revisions were sent to Sepracor by facsimile correspondence on February 25, and March 4, 7, and 9, 2005. In addition, labeling negotiations took place by teleconference on March 2, and 7, 2005. The draft labeling was reviewed by the Clinical, Chemistry, Manufacturing, and Controls, Pharmacology/Toxicology, Clinical Pharmacology and Biopharmaceutics, Statistical, and Project Management teams.

Sepracor submitted revised draft labeling dated March 10, and 11, 2005, for the Package Insert, Patient instructions for use, and carton and container. I compared the draft labeling dated March 10, and 11, 2005, to the Division's requested labeling changes dated February 25, and March 4, 7, and 9, 10, and 11, 2005. The revised draft labeling is identical to the Division's labeling suggestions.

Upon review of the labeling by the Clinical, Chemistry, Manufacturing, and Controls, and Project Management Teams, we agreed with the labeling changes submitted March 10, 2005, (carton and container), and March 11, 2005, (Patient Instructions for Use and 10 (Package Insert).

The draft labeling dated March 10, and 11, 2005, is acceptable.

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

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

FACSIMILE TRANSMITTAL SHEET

Date: February 25, 2005

To: Jerry Klimek Senior Director, Regulatory Affairs	**From:** Akilah Green, RN Regulatory Project Manager
Company: Sepracor Inc.	Division of Pulmonary and Allergy Drug Products
Fax number: 508-357-7491	**Fax number:** 301-827-1271
Phone number: 508-357-7743	**Phone number:** 301-827-5585

Subject: NDA 21-730, Labeling comments

Total no. of pages including cover:

Comments:

Document to be mailed: YES XNO

We have reviewed your draft labeling for the Package Insert and Patient Instructions for Use, for NDA 21-730. Attached are our proposed labeling changes in preparation for the teleconference scheduled for March 2, 2005. In addition, we are providing the following comments to explain some of the changes.

In the clinical trials section:

All statements
were deleted.

Insert figures from Study 051-353 displaying mean percent change in FEV_1 from test-day baseline versus time at Day 1 and Day 56 with corresponding legend, which includes correct n at Visit 2 and Visit 6.

Delete

In the Geriatrics section:

The Geriatrics section was revised in accordance with 21CFR 201.57(f)(10).

Rationale for nonclinical comments regarding the product label:

The recommended changes to the proposed animal to human exposure are based on the parameters detailed below:

Drug:	Xopenex HFA							
	age	mg/dose	# daily doses	mg/day	kg	mg/kg	Factor	mg/m²
Pediatric dose	4	0.045	12	0.54	16	0.03	25	0.84
Adult dose	>12	0.045	12	0.54	50	0.01	37	0.40

	route	mg/kg/day	factor	mg/m²	Dose Ratio Adults	Dose Ratio Children	Rounded Dose Ratio Adults	Rounded Dose Ratio Children
Carcinogenicity:								
rat	dietary	2	6	12	30.03	14.22	30	15
mouse	dietary	500	3	1500	3753.75	1777.78	3800	1800
hamster	dietary	50	4	200	500.50	237.04	500	240
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---
Reproduction and Fertility:								
rat	oral	50	6	300	750.75	N/A	750	N/A
extra			---	---	---	N/A	---	N/A
extra			---	---	---	N/A	---	N/A
extra			---	---	---	N/A	---	N/A
Teratogenicity:								
rabbit	oral	25	12	300	750.75	N/A	750	N/A
mouse	SC	0.25	3	0.75	1.88	N/A	2	N/A
mouse	SC	2.5	3	7.5	18.77	N/A	20	N/A
mouse	SC	0.025	3	0.075	0.19	N/A	1/5	N/A
rabbit	oral	50	12	600	1501.50	N/A	1500	N/A
Overdosage:								
mouse	IV	66	3	198	495.50	234.67	500	230
rat	IV	60	6	360	900.90	426.67	900	430
dog	IH	2.73	20	54.6	136.64	64.71	140	65
extra			---	---	---	---	---	---
Other:	teratogenicity							
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---

The suggested changes to the section describing the results of the genetic toxicology tests are recommended partly to retain consistency with the previously approved Xopenex label. In addition, the chromosome aberration assay in CHO cells conducted with R-, S-, and RS-albuterol did not incorporate the use of adequate test substance concentrations at

the 3 hour evaluation period; the maximum concentrations used did not induce significant cellular toxicity and did not achieve the maximum recommended concentration for the assay. Therefore, the [redacted] was deleted and the results for racemic albuterol were inserted.

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

B

36 Page(s) Withheld

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

_ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

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
2/25/05 11:51:27 AM
CSO

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

FACSIMILE TRANSMITTAL SHEET

Date: February 22, 2005

To: Jerry Klimek **Senior Director, Regulatory Affairs**	**From:** Akilah Green, RN Regulatory Project Manager
Company: Sepracor Inc.	Division of Pulmonary and Allergy Drug Products
Fax number: 508-357-7491	**Fax number:** 301-827-1271
Phone number: 508-357-7743	**Phone number:** 301-827-5585

Subject: NDA 21-730 P/T CMC information request

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES X NO

Your submission dated, May 11, 2004, to NDA 21-730 is currently under review and we have the following comments and requests for information:

The proposed specifications for — are not acceptable.

Available data indicate that — have genotoxic potential. Therefore, in the absence of adequate data to refute the genotoxic or carcinogenic potential of these compounds, the specifications should be reduced to a level which would result in a daily exposure < —/day. Revise the specification to — can for each of these compounds.

The specification for — should be reduced to a level that would result in a maximum daily exposure of — day since there is no adequate data to support the safety of this compound. Revise the specification to — can. Alternately, you can conduct a study (3 months in duration via the inhalation route) to support your proposed specification.

If you have any questions, you may contact Ms. Akilah Green, at 301-827-5585.

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
2/22/05 02:31:45 PM
CSO

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE:	February 22, 2005
TO:	Akilah Green, Regulatory Project Manager Sally Seymour, M.D., Medical Officer, Clinical Reviewer Division of Pulmonary & Allergy Drug Products, HFD-570
THROUGH:	Ni A. Khin, M.D., Branch Chief Good Clinical Practice Branch Division of Scientific Investigations
FROM:	Ele Ibarra-Pratt, RN, MPH Consumer Safety Officer Good Clinical Practice Branch 2, HFD-47 Division of Scientific Investigations
SUBJECT:	Evaluation of Domestic Inspections
NDA:	21-730
SPONSOR:	Sepracor, Inc.
DRUG:	Xopenex (levalbuterol tartrate)™
CHEMICAL CLASSIFICATION:	Type 3, S
THERAPEUTIC CLASSIFICATION:	β_2-receptor agonist
INDICATIONS:	treatment or prevention of bronchospasm in adults, adolescents, and children 4 years of age and older with reversible obstructive airway disease
CONSULTATION REQUEST DATE:	August 25, 2004
GOAL DATE TO PROVIDE INSPECTION SUMMARY:	February 26, 2005
DIVISION GOAL DATE:	March 1, 2005
PDUFA GOAL DATE:	March 12, 2005

I. BACKGROUND:

Levalbuterol tartrate HFA MDI is a β_2-adrenergic receptor agonist in an HFA inhalation aerosol, a new formulation, for the treatment or prevention of bronchospasm in adults, adolescents and children 4 years of age and older with reversible

obstructive airway disease. Levalbuterol hydrochloride (Xopenex®) was initially approved in 1999 and is currently approved as a nebulizer for the treatment or prevention of bronchospasm in adults, adolescents and children 6 years of age and older with reversible obstructive airway disease.

The pivotal studies, sponsored by Sepracor, Inc., were conducted in adolescents 12 years of age and older and adults (protocol 051-353 and 051-355) and children 4-11 years of age (protocol 051-354) with asthma. The primary efficacy endpoint for these studies was the peak in percent change in FEV_1 from baseline, pre-dose, averaged over the 8-week treatment period in protocols 353 and 355 and 28-day treatment period in protocol 354. A total of 445 subjects and 303 subjects were enrolled in protocols 353 and 355, respectively, and 150 subjects in protocol 354. Sites for inspection were selected due to high enrollment; no specific problems were identified during the preliminary review of data.

II. RESULTS (by site):

Name (site)	City, State	Protocol	Insp. Date	EIR Recd.	Classn.	GCP file#
William C. Rees, MD, MBA, FAAP (0201)	Burke, Virginia	353 355	12/14-23/2004	2/7/2005	NAI	11400
Andrew J. Pedinoff, MD (0017)	Princeton, New Jersey	353 354	11/29- 12/13/2004	1/11/2005	NAI	9181
Angelique Barreto, MD (1000)	Oklahoma City, Oklahoma	354	11/3-11/15/2004	12/03/2004	VAI	11347

The following protocols were audited:

Protocol 051-353: "An Efficacy and Safety Study of Levalbuterol, Racemic Albuterol and Placebo in Subjects Twelve Years of Age and Older with Asthma"

Protocol 051-354: "An Efficacy, Safety, and Tolerability Study of Daily Dosing with Levalbuterol, Racemic Albuterol, and Placebo in Pediatric Subjects with Asthma "

Protocol 051-355: "An Efficacy and Safety Study of Levalbuterol, Racemic Albuterol and Placebo in Subjects Twelve Years of Age and Older with Asthma"

The pivotal studies were conducted in adolescents 12 years of age and older and adults (protocol 051-353 and 051-355) and children 4-11 years of age (protocol 051-354) with asthma. Protocols 353 and 355 were double-blind, randomized, placebo and active controlled, multicenter, parallel-group trial, which consisted of one-week single-blind placebo run-in period and 8-week double-blind treatment period. The treatment groups were randomized to levalbuterol HFA-B (B=manufactured at — site) 90 mcg QID, proventil HFA 180 mcg QID, and placebo 2 actuations QID. In protocol 355, levalbuterol HFA-A (A=manufactured at 3M) was included as one of the treatment groups. Protocol 354 was a double-blind, randomized, placebo and active-controlled, multicenter, parallel-group study in children 4-11 years of age with asthma. Subjects entered a one-week single-blind placebo run-in period followed by a 28-day treatment period with either levalbuterol HFA-A 90 mcg QID or placebo 2 actuations QID. Subject eligibility include documented diagnosis of asthma for at least 6 months as defined by the American Thoracic Society and FEV1 >45% and <80% in children and >45% and <75% in adolescents and adults, with a >12% reversibility. The primary efficacy endpoint for these studies was the peak in percent change in FEV1 from baseline, pre-dose, averaged over the 8-week treatment period in protocols 353 and 355 and 28-day treatment period in protocol 354. Safety assessments include reports of adverse events, clinical labs, physical evaluations, vital signs, ECGs, plasma concentrations in a subset of subjects, rescue medication use, asthma control and asthma attacks, and paradoxical bronchoconstriction. A total of 445 subjects and 303 subjects were enrolled in protocols 353 and 355, respectively, and 150 subjects in protocol 354. Sites were selected due to high enrollment; no specific problems were identified during the preliminary review of data.

(1) William C. Rees, MD, MBA, FAAP (site 0201)

PI-Coor Clinical Research, L.L.C.
8982 Fern Park Drive
Burke, Virginia 22015

Protocols 051-353 (26 enrolled) and 051-355 (25 enrolled) were audited. The inspection reviewed case report forms, data listings and source documents. Source documents included progress notes, IRB and sponsor correspondences, drug accountability records, lab reports, medical history records, spirometry reports, informed consent documents and adverse event records. The data listings from the review division were verified with on site documentation for selected subjects; no significant deviations were identified.

The inspection found that Dr. Rees was in compliance with applicable regulations and no 483 was issued. There were no discrepancies noted with the data listings (e.g., FEV_1 values) provided by HFD-570, as verified with source documents on site. The inspection is classified NAI. Data at this site appear acceptable.

(2) Andrew J. Pedinoff, MD (site 0017)
Princeton Center for Clinical Research
414 Executive Drive
Princeton, New Jersey 08540

Protocols 051-353 and 051-354 were audited at this site. The inspection reviewed case report forms, data listings and source documents. Source documents included screening records, lab reports, medical history records, spirometry reports, informed consent documents and adverse events. The data listings from the review division were verified with on site documentation for selected subjects; no significant findings were identified.

For protocol 051-353, a total of 23 subjects were screened, 3 screen failures, 20 subjects randomized, 5 subject discontinued, and 15 subjects completed study. A total of 10 subject records (401-404, 408, 593-595, 657, and 659) were reviewed during the inspection and no significant discrepancies were found. For protocol 051-354, a total of 4 subjects were screened, one screen failure, 3 subjects randomized, and 3 subjects completed study. All 4 subjects records (001-005) were reviewed during the inspection and no significant discrepancies were found.

The inspection found that Dr. Pedinoff was in compliance with applicable regulations and no 483 was issued. There were no discrepancies noted with the data listings (e.g., FEV_1 values) provided by HFD-570, as verified with source documents on site. The inspection is classified NAI. Data at this site appear acceptable.

(3) Angelique Barreto, MD (1000)
Sooner Clinical Research
5929 North May Avenue, Suite 401
Oklahoma City, Oklahoma 73112Concepcion, Chile

Dr. Barreto conducted protocol 051-354 and enrolled a total of 10 subjects; 5 subjects completed the study. The audit reviewed 7 of the 10 subjects enrolled. The inspection reviewed source documents, case report forms, consent forms, spirometry printouts, ECGs, and protocol required evaluations.

All of the data points generated from HFD-570 were verified on site with the source documents and no significant differences were found. However, there were problems noted with the spirometer that was newly purchased by the investigator for use in the study that may impact the validity of the FEV1 values reported from this site. These problems include: (1) the spirometer was not calibrated according to the ATS guidelines; it appeared that the spirometer was calibrated once prior to the start of the study, (2) duplicate spirometry printouts were found for two or three attempts and the duplicates were found in subsequent visits due to the spirometer not printing poor efforts and printing prior successful efforts or the site failing to successfully clear the memory of the machine, and (3) the two best efforts were not always within $\pm$ 5% difference between the subject's best efforts. In addition, the site claimed that it was difficult to get kids to produce three maneuvers every 15 minutes with evaluations being performed in between maneuvers and that it

was difficult to get the kids to blow hard enough to get a good reading.

The inspection documented that Dr. Barreto did not maintain adequate and accurate recordkeeping, in violation of 312.62(b), and did not adhere to the investigational plan, in violation of 21 CFR 312.60. The following violations were confirmed:

1) Protocol violations [21 CFR 312.60].

   a. The protocol required that spirometry measurements be collected and standardized according to the American Thoracic Society (ATS) guidelines. The guidelines recommend that the spirometer be checked at least daily with a calibrated syringe to test the spirometer's ability to accurately measure volume. Our investigation found that the spirometer used during the study was calibrated once at the start of the study. In addition, Dr. Barreto did not consistently perform three maneuvers for spirometry testing, as recommended by the ATS guidelines.

   b. The protocol required that a chest x-ray be obtained at screening if one has not been performed within 12 months of study visit 1. Chest x-rays were not performed for subjects 208, 273 and 293 until after the subjects were randomized into the study.

   c. The protocol inclusion criteria required that subjects have a chest x-ray that is not diagnostic of pneumonia, atelectasis, pulmonary fibrosis, pneumothorax, chronic obstructive pulmonary disease, etc. The baseline chest x-ray performed on 5/14/03 for subject 293 documented a "band of discoid or platelike atelectasis in the right mid to upper lung." Subject 293 did not meet inclusion criteria but was randomized into the study on 4/26/03, before the x-ray was performed.

   d. The protocol inclusion criteria required that subjects demonstrate $\geq$ 12% reversibility of airflow obstruction within 15-30 minutes following inhalation of racemic albuterol at screening. Subjects 274 and 294 demonstrated a reversibility of, 3% and -16%, respectively, but were both randomized into the study.

2) Recordkeeping violations [21 CFR 312.62(b)].

   a. There were duplicate spirometry test results for multiple maneuvers and for spirometry testing performed at subsequent study visits for subjects 206, 274, and 293.

   b. Subject 273 was not administered Flovent or Advair during the study, however, the concomitant medication case report form recorded that the subject was administered these medications during the study.

In summary, the most significant violations were attributed to the spirometer machine, as noted above. The investigator provided a response and proposed corrective actions to prevent similar violations from recurring. Therefore, DSI issued an untitled letter, VAI with response accepted.

Given the problems and violations identified above, HFD-570 may want to consider the potential impact the findings may have on the validity or accuracy of the FEV_1 values that were reported from this site.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

In conclusion, two (Drs. Rees and Pedinoff) of the three sites inspected adhered to the applicable regulations governing the conduct of clinical investigations. The inspection of documents support that audited subjects exist, met eligibility criteria, received assigned study medication, adhered to protocol and signed informed consent. However, a number of deviations were noted at Dr. Barreto's site (1000), as noted herein.

In general, the data submitted in support of this NDA appear to be acceptable. However, DSI recommends that HFD-570 consider the potential impact the findings from site 1000 may have on the validity or accuracy of the FEV_1 values that were reported from this site.

Follow-up action: None needed.

{See appended electronic signature page}
Ele Ibarra-Pratt, R.N., M.P.H.
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

CONCURRENCE:

Supervisory comments

{See appended electronic signature page}
Ni A. Khin, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

DISTRIBUTION:
NDA 21-730
HFD-45/Division File
HFD-45/Reading File
HFD-45/Program Management Staff (electronic copy)
HFD-47Ball/Khin
HFD-47/Pratt/GCPB2 Files

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

/s/

Elinita Ibarra-Pratt
2/22/05 01:33:36 PM
CSO

Ni Aye Khin
2/22/05 01:42:41 PM
MEDICAL OFFICER

84 Waterford Drive
Marlborough, MA 01752

Phone: (508) 481-6700
Fax: (508) 357-7491

FAX COVER SHEET

TO: Akilah Green Senior Regulatory Manager	FROM: Jerry Klimek
Company: FDA, CDER, ODEII Div. of Pulmonary Drug Prod.	Title: Senior Director Regulatory Affairs
Phone: (301) 827-1050	Phone: (508) 357-7743
Fax: (301) 827-1271	Fax: (508) 357-7491

Date: February 22, 2005
Pages: 3 (including this cover sheet)
Re: **NDA 21-730 Xopenex HFA™ (levalbuterol tartrate) Inhalation Aerosol**
Amendment to a Pending Application: Response to FDA Request for Information dated February 8, 2005

MESSAGE

Dear Ms. Green;

Attached is a copy of the amendment submitted to the Agency today. The submission should arrive at the Central Document Room tomorrow (Wednesday, February 23, 2005).

Sincerely,

Jerry Klimek
Senior Director, Regulatory Affairs

SEPRACOR

February 22, 2005

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

Re: **NDA 21-730**
Xopenex HFA™ (levalbuterol tartrate) Inhalation Aerosol
Amendment to a Pending Application: Response to FDA Request for Information dated February 8, 2005

Dear Dr. Chowdhury:

Please reference Sepracor Inc.'s pending NDA 21-730 for Xopenex HFA™ (levalbuterol tartrate) Inhalation Aerosol submitted on May 11, 2004. Please also reference the FDA facsimile dated February 8, 2005, in regard to a Clinical Pharmacology and Biopharmaceutics Information Request for information on the metabolism, elimination, and effect of renal and hepatic impairment on the pharmacokinetics of (R)-albuterol.

The purpose of this submission is to provide a response to the request detailed in the facsimile dated February 8, 2005.

Format and Structure of the Amendment

This NDA amendment is being submitted in electronic format as described in the CDER guidance entitled *Guidance for Industry: Providing Regulatory Submissions in Electronic Format – NDAs;* IT 3, January 1999. The archival copy of the amendment comprises the following:

1. One CD-ROM containing the entire amendment in electronic format. The amendment is approximately 3.5 MB in size and is located in folder *N21730*. The files on the CD-ROM have been scanned for viruses with Network Associates VirusScan Enterprise 7.1.0 with a Virus Definition of 4431 dated February 21, 2005. The electronic archival copy will serve as the electronic review copy.

2. One paper volume containing the Table of Contents (Amendment Index) and the original signed Cover Letter and Form FDA 356h.

The following table lists the components of this amendment and provides the folder and file name for each component:

Description	Location
Cover Letter	*N21730\cover.pdf*
Form FDA 356h	*N21730\356h.pdf*
Table of Contents (Amendment Index)	*N21730\amendtoc.pdf*
Response to Clinical Pharmacology Comment	*N21730\hpbio\hpsum.pdf*
Publications	*N21730\hpbio\pubs\...*

If further information is needed, please contact me by telephone at (508)-357-7743 or by fax at (508) 357-7491.

Sincerely,

Jerry Klimek
Senior Director, Regulatory Affairs

Copy Cover Letter only: Ms. Akilah Green

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

FACSIMILE TRANSMITTAL SHEET

DATE: February 15, 2005

To: Jerry Klimek Associate Director, Regulatory Affairs	**From: Akilah Green** **Regulatory Project Manager**
Company: Sepracor	Division of Pulmonary and Allergy Drug Products
Fax number: 508-357-7491	**Fax number:** 301-827-1271
Phone number: 508-357-7743	**Phone number:** 301-827-5585

Subject: NDA # 21-730

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES xNO

Your submission dated, May 11, 2004, to NDA 21-730 is currently under review and we have the following requests:

Submit the following figures by February 23, 2005.

- Mean percent change in FEV1 from study baseline versus time at Visit 2 and Visit 6 in Study 051-353.

- Mean percent change in FEV1 from study baseline versus time at Visit 2 and Visit 6 in Study 051-354.

- Mean percent change in FEV1 from study baseline versus time at Visit 2 and Visit 6 in Study 051-355.

- Mean percent change in FEV1 from test day baseline in Study 051-355 versus time at Visit 2 and Visit 6 with the data from the levalbuterol HFA-A and levalbuterol HFA-B groups combined.

- Mean percent change in FEV1 from study baseline in Study 051-355 versus time at Visit 2 and Visit 6 with the data from the levalbuterol HFA-A and levalbuterol HFA-B groups combined.

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

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
2/15/05 02:18:31 PM
CSO

C

4 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: February 8, 2005

To: Jerry Klimek **Senior Director, Regulatory Affairs**	**From:** Akilah Green, RN Regulatory Project Manager
Company: Sepracor Inc.	Division of Pulmonary and Allergy Drug Products
Fax number: 508-357-7491	**Fax number:** 301-827-1271
Phone number: 508-357-7743	**Phone number:** 301-827-5585

Subject: NDA 21-730 Clinical Pharmacology and Biopharmaceutics Information Request

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES X NO

NDA 21-730

Your submission dated May 12, 2004, to NDA 21-730 is currently under review and we have the following request for information:

> Provide information on the metabolism, elimination, and effect of renal and hepatic impairment on the pharmacokinetics of R-albuterol. This information may come from previously completed studies, from the medical literature, or from new clinical pharmacology studies. This information is needed to update the labeling for your product with regards to the effect of intrinsic factors on the clinical pharmacology of the drug. This information should be submitted before February 27, 2005.

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

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
2/8/05 12:14:13 PM
CSO

D

4 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: January 7, 2005

To: Jerry Klimek **Associate Director, Regulatory Affairs**	**From:** Akilah Green, RN Regulatory Project Manager
Company: Sepracor Inc.	Division of Pulmonary and Allergy Drug Products
Fax number: 508-357-7491	**Fax number:** 301-827-1271
Phone number: 508-357-7743	**Phone number:** 301-827-5585

Subject: NDA 21-730

Total no. of pages including cover: 9

Comments:

Document to be mailed: XYES NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-730

INFORMATION REQUEST LETTER

Sepracor, Inc.
84 Waterford Drive
Marlborough, Massachusetts 01752-7010

Attention: Jerry Klimek
Associate Director, Regulatory Affairs

Dear Mr. Klimek:

Please refer to your May 11, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xopenex (levalbuterol) HFA.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Revise the test method for optical rotation to obtain — in order to detect appreciable enantiomeric content.
2. Clarify which analytical procedure is used for confirmatory identity testing of the — ethanol used in the manufacture of the drug substance.
3. ' — ' is not acceptable for — —). Delete the reference to ' — from this particular manufacturing process.
4. Confirm that testing will be performed by the drug product manufacturer on the drug substance. Per 21 CFR 211.84, the manufacturer must perform an identity test on the drug substance, at minimum. In addition, confirmatory testing for Particle Size should be performed on the drug substance to ensure acceptable Aerodynamic Particle Size Distribution in the drug product.
5. Provide information on the — (used to prepare the product bulk formulation) — and at the processing temperature — at minimum.
6. Provide the in-process controls and master batch records for the assembly of actuators onto the canisters.
7. Provide data to show that the in-process control of — s adequate for the

8. Provide data to show that the —

9. Provide data to show that the — is sufficient for the detection of —

10. In the drug product specification, regroup the Aerodynamic Particle Size Distribution as follows: —

11. Include Identification for — in the drug product specification.

12. In order to justify the use of — as part of the drug product specification, provide these test methods used for incoming components.
— s are not included in the NDA, and the test method for — is Method — used for the finished MDI (i.e., filled with the drug product formulation).

13. Revise — acceptance criteria in the drug product specification to be in units of —

14. Revise the — in the drug product specification to reflect release and stability data (e.g., —

15. Provide a post-approval agreement for the integration of a dose counting mechanism in the MDI.

16. Submit revised labeling incorporating the following preliminary revisions. Additional comments may be forwarded when the reviews are completed:

Package insert:

e

5 Page(s) Withheld

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

_ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

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

/s/

Richard Lostritto
1/5/05 05:39:24 PM

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

FACSIMILE TRANSMITTAL SHEET

DATE: December 22, 2004

To: Jerry Klimek Associate Director, Regulatory Affairs	Akilah Green **From:** Regulatory Project Manager
Company: Sepracor	Division of Pulmonary and Allergy Drug Products
Fax number: 508-357-7491	**Fax number:** 301-827-1271
Phone number: 508-357-7743	**Phone number:** 301-827-5585

Subject: NDA 21-730 Information Request

Total no. of pages including cover: 3

To:

Document to be mailed: YES xNO

NDA 21-730
Xopenex HFA

Your submission dated May 11, 2004, to NDA# 21-730, is currently under review and we have the following requests:

In the Protocol Deviations section of your study reports, you report the number of subjects who used a disallowed medication. You state many of the protocol violations were for beta agonists with common violations being insufficient washout for beta agonist prior to Visit 1, use of beta agonist during the study period, and restart of the beta agonist at Visit 6.

1. Provide the number of subjects in Studies 051-353, 051-354, and 051-355 for each of the following beta agonist protocol violations:

   - insufficient washout for beta agonist prior to Visit 1
   - use of beta agonist during the study period
   - restart of the beta agonist at Visit 6.

2. Clarify what qualified as the restart of beta agonist at Visit 6.

3. Clarify if the use of study rescue medication counted as a protocol violation.

4. Submit the expiration dates for the active control and rescue medications used in Studies 051-353, 051-354, and 051-355.

5. Submit a brief summary of the postmarketing safety experience with levalbuterol inhalation solution.

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

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
12/22/04 02:17:31 PM
CSO

CONSULTATION RESPONSE

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

DATE RECEIVED: June 24, 2004	**DESIRED COMPLETION DATE:** December 1, 2004 **PDUFA DATE:** March 12, 2005	**ODS CONSULT #:** 04-0180

TO: Badrul Chowdhury, MD
Director, Division of Pulmonary and Allergy Drug Products
HFD-570

THROUGH: Akilah Green
Project Manager, Division of Pulmonary and Allergy Drug Products
HFD-570

PRODUCT NAME:	**NDA SPONSOR:**
Xopenex HFA (Levalbuterol Tartrate Inhalation Aerosol) 45 mcg/actuation **NDA #: 21-730**	Sepracor, Inc.

SAFETY EVALUATOR: Linda M. Wisniewski, RN

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Xopenex 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 label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name Xopenex HFA acceptable from a promotional perspective.

Denise Toyer, PharmD.
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Carol Holquist, RPh
Director
Division of Medication Errors and Technical Support
Office of Drug Safety

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: September 3, 2004

NDA#: 21-730

NAME OF DRUG: **Xopenex HFA**
(Levalbuterol Tartrate Inhalation Aerosol)

NDA HOLDER: Sepracor, Inc.

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, "Xopenex HFA", regarding potential name confusion with other proprietary or established drug names. The sponsor is currently marketing Xopenex as an inhalation solution available in the following strengths: 0.0103%, 0.021%, 0.042%, and 0.25%. These products were approved on 1/30/02, 3/25/99, 3/25/99, and 7/18/03, respectively. However, this product is not currently available in a formulation that contains Chlorofluorocarbon (CFC). Therfore, Xopenex HFA will be an addition to the the Xopenex product line. Draft container labels, carton, and insert labeling were provided for review and comment.

PRODUCT INFORMATION:

Xopenex HFA contains the active ingredient levalbuterol tartrate, the (R)-enantiomer of albuterol. It is a pressurized metered-dose aerosol inhaler (MDI), which produces an aerosol for oral inhalation. Xopenex HFA is indicated for the treatment or prevention of bronchospasm in adults, adolescents, and children four years of age and older with reversible obstructive airway disease. For treatment of acute episodes of bronchospasm or prevention of asthmatic symptoms, the usual dosage of Xopenex HFA for adults and children four years of age and older is two inhalations (90 mcg) repeated every four to six hours; in some patients, one inhalation every four hours may be sufficient. It is recommended to prime the inhaler before using for the first time and in cases where the inhaler has not be used for more than — by releasing four test sprays into the air, away from the face. To maintain proper use of this product, it is critical that the actuator be washed and dried thoroughly at least once a week. The inhaler may cease to deliver medication if not properly cleaned and dried thoroughly. It is supplied as a pressurized aluminum canister with a blue plastic actuator and red cap packaged together in a box with patient's instructions. The canister is labeled with a net weight of 15 g and contains 200 metered inhalations. Flunisolide hemihydrate in HFA is a solution formulation that does not contain chlorofluorcarbons (CFCs) as the propellant.

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 databases[3] for existing drug names which sound-alike or look-alike to Xopenex 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 conducted[4]. The Saegis[5] 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 healthcare 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 Xopenex HFA. Potential concerns regarding drug marketing and promotion related to the proposed name were 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 proposed proprietary name Xopenex HFA acceptable from a promotional perspective.

2. The Expert Panel identified two proprietary names that were thought to have the potential for confusion with Xopenex 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	Dosage form(s), Established name	Usual adult dose*	Other**
Xopenex HFA	Levalbuterol Tartrate Inhalation Aerosol 45 mcg/inhalation	Two inhalations every four to six hours.	N/A
Xopenex	Levalbuterol Hydrochloride Solution for Inhalation: 0.021%, 0.042%, 0.0103%, and 0.25%	0.63 mg to 1.25 mg every six to eight hours	LA/SA
Vaponephrine/ Vaponefrin	Racemic Epinephrine	Continuous or every six hours.***	LA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike) ***Further dosing information is not available.			

[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] 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.
[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. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. No additional names of concern were identified in POCA that were not discussed in EPD.

C. ADVERSE EVENT REPORTING SYSTEM (AERS)

Xopenex has been marketed since March 25, 1999, thus, DMETS searched the FDA Adverse Event Reporting System (AERS) for all post-marketing safety reports of medication errors associated with Xopenex. The MEDDRA Preferred Terms (PT) "Medication Error", "Accidental Overdose", and "Overdose NOS" and the terms "Xopenex", "Levalbuterol Tartrate", "Xop%", and "Leval%" were used as search criteria. This search strategy retrieved a total of fifty-five cases (55) involving Xopenex. They include seven actual errors and forty-eight potential errors. One actual error involved the accidental ingestion of Xopenex by a child. No outcome information is provided for this case. The remaining six actual and forty-eight potential cases involved confusion between the [redacted] packaging of Xopenex and Accuneb, Pulmicort, Duoneb, Atrovent, Tobramycin, Pulmozyme, Cromolyn, and Donvase. DMETS has conducted a post-marketing review concerning the issue of confusion with [redacted] vials (see ODS Consult #02-0048). There continues to be discussion between DMETS, OND, and other constituents pertaining to a solution for this safety concern.

D. 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 Xopenex 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 Xopenex HFA (see page 5). 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
Outpatient RX: Xopenex HFA 2 puffs q4-6hrs #1	Xopenex HFA 10 mg Sig: 1 po qd # 30
Inpatient RX: start Xopenex HFA 2 inhalations Q4-6hrs on 6/22/04	

2. Results:

Two of the respondents interpreted the proposed name as Zofranex HFA which sounds similar to the currently marketed product Zofran. Additionally, one respondent from the verbal study interpreted the proposed name as Zolpidex HFA, which sounds similar to the currently marketed product Zolpidem. See appendix A for the complete listing of the interpretations from the verbal and written studies.

E. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Xopenex HFA, the primary concerns related to potential look-alike and/or sound-alike confusion with Xopenex and Vaponephrine/Vaponefrin. Vaponephrine/Vaponefrin will not be discussed further because it was withdrawn by the commissioner on April 5, 1985. Safety concerns related to the "HFA" modifier were also considered due to the possibility of omission of the modifier or incorporation of it into the scripted presentation of the name of the product.

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that Xopenex HFA could be confused with Xopenex. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Xopenex.

1. Look-alike and Sound-alike concerns:

   a. Xopenex HFA is the latest product extension to Xopenex. Xopenex is a currently approved drug product and DMETS is concerned that Xopenex HFA might be confused with Xopenex (levalbuterol hydrochloride solution for inhalation). Since both products share the root name (Xopenex), there was concern that confusion might occur between these products if the modifier was omitted. The potential harm to the patient is minimal given the products have the same indication of use and active ingredients but different salts (lebalbuterol hydrochloride vs. levalbuterol tartrate) and are different formulations. If an order for Xopenex HFA were written and misinterpreted as Xopenex, or vice versa, the strengths will help to differentiate the two products. Once two dosage forms (inhalation solution and inhalation aerosol) are marketed, practitioners will need to further clarify which dosage form and strength is being ordered for the patient. There will need to be an education campaign to alert health care practitioners to the new dosage formulation including product differences.

b. Two of the respondents in the verbal prescription studies interpreted the proposed name as Zofranex HFA. These responses sound similar to the currently marketed product Zofran. The names Zofran and Xopenex sound similar to each other because the letters 'xo' are pronounced like 'zo' and both may utilize a long 'o' such as in 'zone'. The potential for confusion may be minimized by the presence of the modifier "HFA" in association with the proprietary name Xopenex. Even if the modifier were omitted, Zofran exists in multiple dosage forms (e.g. injection, orally disintegrating tablets, oral solution and tablets), and strengths (2 mg/mL, 4 mg/5 mL, 32 mg/50 mL, 4 mg, and 8 mg) which will further distinguish the two products. Additionally, DMETS has not received any reports of confusion involving Zofran and Xopenex.

c. One respondent in the verbal prescription studies interpreted the proposed name as Zolpidex HFA. This response sounds similar to the currently marketed product Zolpidem. The names Xopenex and Zolpidem sound similar to each other because the letters 'xo' are pronounced like 'zo' and both may utilize a long 'o', such as in 'zone'. The potential for confusion may be minimized by the presence of the modifier 'HFA" in association with the proprietary name Xopenex. Even if the modifier were omitted, Zolpidem exists in two strengths (5 mg and 10 mg) and one dosage form (tablet) which will further distinguish the two products. Additionally, DMETS has not received any reports of confusion involving Zolpidem and Xopenex.

d. One respondent in the verbal prescription studies interpreted the proposed name as Dosenex HFA. This response sounds similar to the currently marketed product Desenex. The names Xopenex and Desenex sound similar to each other due to the fact that both names end with the same four letters (enex). However, the beginnings of each name are phonetically different. The potential for confusion may be minimized by the presence of the modifier 'HFA' in association with the proprietary name Xopenex. Even if the modifier were omitted, Desenex exists in topical over-the-counter dosage forms (soap, cream, spray powder, spray liquid, and powder) which will further distinguish the two products. Additionally, DMETS has not received any reports of confusion involving Desenex and Xopenex.

2. Modifier (HFA) concerns:

Historically, sponsors have used the modifier "HFA" to distinguish between a new HFA containing formulation and their existing "metered dose inhalers" that contain the propellant "chlorofluorcarbon" (CFC). Since Xopenex exists in only one dosage form, solution for inhalation, and does not have a "chlorofluorcarbon" (CFC)-containing product from which it would need to distinguish Xopenex HFA, DMETS questions the need for the modifier. However, without the 'HFA' modifier, practitioners may think that Xopenex is a chlorofluorcarbon (CFC) containing product. Post-marketing experience has demonstrated that modifiers are often omitted especially if practitioners feel they are not needed to distinguish a product. The Xopenex inhalation solution and metered-dose-inhaler have different strengths which will help to mitigate confusion. Since the modifier does not provide any differentiating characteristics, there is the potential that it will be omitted. The dosage forms (Metered Dose Inhaler vs. Inhalation Solution) and the strength are likely to be more differentiating product characteristics that will help mitigate confusion. In summary,

although DMETS feels that the HFA modifier may not be a differentiating factor, it has no objection to its use in the proprietary name.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In review of the container labels, carton and insert labeling of Xopenex HFA, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENT

1. Increase the font of the established name so that it is at least ½ the size of the proprietary name. See 21 CFR 201.10(g)(2).

2. The lettering on the background is difficult to read and may lead to errors. DMETS recommends using a color combination that provides sufficient contrast and greater readability.

3. The graphic is distracting and interferes with the readability of the name (see below). We recommend deleting as it appears to serve no purpose.

B. CONTAINER LABELING

See General Comments A1 through A3.

C. CARTON LABELING

See General Comments A1 through A3.

D. INSERT LABELING

See General Comment A1.

E. PATIENT PACKAGE INSERT

No comment.

IV. RECOMMENDATIONS:

A. DMETS has no objections to the use of the proprietary name, Xopenex 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.

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 Xopenex 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.

Linda M. Wisniewski, RN
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Appendix A:

Xopenex HFA
NDA: 21-720
ODS Consult: 04-0049

Written Inpatient	**Written Outpatient**	**Verbal**
Xopenex HFA	Topenex HFA	Dilfinex
Xopenex HFA	Xopenex HAD	Dosenex HAS
Xopenex HFA	Xopenex HFA	Xopenex HFA
Xopenex HFA	Xopenex HFA	Xopenex HFA
Xopenex HFA	Xopenex HFA	Xopenex HFA
Xopenex HFA	Xopenex HFA	Xopenex HFA
Xopenex HFA	Xopenex HFA	Xopenex HFA
Xopenex HFA	Xopenex HFA	Xopenex HFA
Xopenex HFA	Xopenex HFA	Xopenex hfa
Xopenex HFA	Xopenex HFA	Zofenex
Xopenex HFA	Xopenex HFA	Zofinex HFA
Xopenex HFA	Xopenex HFA	Zofranex HFA
Xopenex HFA	Xopenex HFA	Zofranex HFA
Xopenex HFA	Xopenex HFA	Zolpenex HFA
Xopenex HFA	Xopenex HFA	Zolpidex HFA
Xopenex HFA	Xopenex HFA	Zopennex HAS
Xopenex HFA		Zopinex HFA
Xopenex JFA		Zopinex HSA

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

/s/

Linda Wisniewski
11/17/04 02:38:06 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
11/17/04 03:15:46 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
11/17/04 04:00:13 PM
DRUG SAFETY OFFICE REVIEWER

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

FACSIMILE TRANSMITTAL SHEET

DATE: September 28, 2004

To: Jerry Klimek	Akilah Green **From:** Regulatory Project Manager
Company: Sepracor	Division of Pulmonary and Allergy Drug Products
Fax number: 508-357-7491	**Fax number:** 301-827-1271
Phone number: 508-357-7743	**Phone number:** 301-827-5585

Subject: NDA 21-730 Information Request

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES xNO

NDA 21-730
Xopenex HFA

Your submission dated May 11, 2004, to NDA 21-730, is currently under review and we have the following request:

> Provide data sets and NONMEM control stream files and output files as SAS transport files, generated from the population PK analysis for levalbuterol and S-albuterol

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

_____
Akilah Green, Regulatory Project Manager

Drafted by:	Green/September 21, 2004
Initialed by:	Barnes/September 23, 2004
	Suarez-Sharp/September 27, 2004
	Kim, S. for Fadiran/September 27, 2004
Finalized:	Green/September 28, 2004

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
9/28/04 01:47:26 PM
CSO

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

FACSIMILE TRANSMITTAL SHEET

DATE: August 10, 2004

To: Jerry Klimek	Akilah Green **From:** Regulatory Project Manager
Company: Sepracor	Division of Pulmonary and Allergy Drug Products
Fax number: 508-357-7491	**Fax number:** 301-827-1271
Phone number: 508-357-7491	**Phone number:** 301-827-5585
Subject: NDA 21-730 Information Request	
Total no. of pages including cover: 3	

Comments:

Document to be mailed: YES xNO

NDA 21-730
Xopenex HFA

Your submission dated May 11, 2004, to NDA 21-730, is currently under review and we have the following request:

> The Case Report Tabulations (CRTs) for Study 051-355 appear to be incomplete. For example: crt\datasets\051-355\PFT.XPT, crt\datasets\051-355\PFT1.XPT, and crt\datasets\051-355\PFT2.XPT do not contain complete data for the pulmonary function variables. Review the database for Study 051-355 and resubmit the complete datasets.

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

_____

Akilah Green, Regulatory Project Manager

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
8/10/04 03:10:15 PM
CSO

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

FACSIMILE TRANSMITTAL SHEET

Date: August 10, 2004

To: Jerry Klimek	**From:** Akilah Green, RN Regulatory Project Manager
Company: Sepracor Inc.	Division of Pulmonary and Allergy Drug Products
Fax number: 508-357-7491	**Fax number:** 301-827-1271
Phone number: 508-357-7491	**Phone number:** 301-827-5585

Subject: NDA 21-730 Statistical comments

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES XNO

NDA 21-730
Xopenex HFA

Your submission dated May 12, 2004, is under review and we have the following requests for information:

1. In the study report of Study 051-308 and protocol there is mention of spirometry after exercise challenges following two single blind placebo MDI administrations at baseline (Visit 2). With the exception of section 9.5.1.2.1, where the use of an exercise challenge is implied, there is no mention of an exercise challenge after pirbuterol MDI at Visit 2. Was there an exercise challenge after pirbuterol? Explain.

2. In Study 051-312 you state that some subjects received doses 2X, 2X, 2X rather than 1X, 2X, 4X. Explain how this was possible.

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

Akilah Green, Regulatory Project Manager

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
8/10/04 03:05:47 PM
CSO

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

FACSIMILE TRANSMITTAL SHEET

Date: May 19, 2004

To: Renee Carroll **Associate Director, Regulatory Affairs**	**From:** Akilah Green, RN Regulatory Project Manager
Company: Sepracor Inc.	Division of Pulmonary and Allergy Drug Products
Fax number: 508-357-7491	**Fax number:** 301-827-1271
Phone number: 508-357-7598	**Phone number:** 301-827-5585

Subject: NDA 21-730 Acknowledgement Letter

Total no. of pages including cover: 4

Comments:

Document to be mailed: XYES NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-730

Sepracor Inc.
84 Waterford Drive
Marlborough, Massachusetts

Attention: Renee Carroll
Associate Director, Regulatory Affairs

Dear Ms. Carroll:

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:	Xopenex (levalbuterol tartrate) HFA
Review Priority Classification:	Standard (S)
Date of Application:	May 11, 2004
Date of Receipt:	May 12, 2004
Our Reference Number:	NDA 21-730

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 July 11, 2004, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be March 12, 2005.

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/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Drug Products, HFD-570
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Akilah Green, Regulatory Project Manager, at 301-827-5580.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Supervisory CSO
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 this page is the manifestation of the electronic signature.

/s/

Akilah Green
5/19/04 02:46:47 PM
Signed for Sandy Barnes

ORIGINAL

SEPRACOR

RECEIVED
MAY 12 2004
CDR / CDER

May 11, 2004

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

RECEIVED
MAY 13 2004
FDR/CDER

Re: **NDA 21-730**
Xopenex HFA™ (levalbuterol tartrate HFA) Inhalation Aerosol
Original New Drug Application

Dear Dr. Chowdhury:

Pursuant to Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, Sepracor Inc. is hereby submitting an original New Drug Application for Xopenex HFA™ (levalbuterol tartrate HFA) Inhalation Aerosol for the treatment or prevention of bronchospasm in adults, adolescents, and children 4 years of age and older with reversible obstructive airway disease.

Levalbuterol is the therapeutic enantiomer ((R)-isomer) of a commonly used selective beta agonist, racemic albuterol. The levalbuterol active moiety has also been widely used in the United States since FDA approval of Xopenex Inhalation Solution (NDA 20-837) on March 25, 1999, wherein levalbuterol is provided as a hydrochloride salt.

This NDA application contains data from 12 Phase II and Phase III clinical trials (conducted under IND 62,906), including two pivotal studies in adults and adolescents (051-353 and 051-355) and one pivotal study in children age 4 and older (051-354). These studies provided justification for the dose selected for marketing (90 μg QID) and demonstrated that the to-be-marketed dose is safe and effective for the proposed indication.

The following data are being incorporated by reference, based on prior agreement with the Agency: (1) The long-term clinical safety data for Proventil® HFA Inhalation Aerosol, provided to FDA in NDA 20-503, are incorporated into this application based on a direct right-of-reference for this purpose granted by 3M Pharmaceuticals; and (2) all relevant toxicology, human safety, human efficacy, and other data provided to FDA in NDA 20-837 (submitted and owned by Sepracor Inc.) for Xopenex® Inhalation Solution are incorporated by reference into this application. Additionally, carcinogenicity data for racemic albuterol provided to FDA in NDA 19-243 for Proventil® Inhalation Solution are relied upon under 21 USC 355(b)(2) based on a prior agreement with the Agency.

Reference is made to meetings held with the Agency on October 29, 2003, and on January 5, 2004, during which requirements for the evaluation of device performance were discussed and agreed upon. The data obtained to date and provided in this application indicate that the Xopenex HFA device manufactured for us by 3M Pharmaceuticals performs consistently and satisfactorily, and in a manner comparable to the Proventil HFA device manufactured in the same facility. Sepracor commits to provide additional device performance data with the 120-Day Safety Update, as discussed at the January 5, 2004, teleconference.

Information concerning patents is provided in Sections 13 and 14 of this submission. Information on 11 US patents (Nos. 5,362,755; 5,547,994; 5,760,090; 5,844,002; 6,083,993; 5,836,299; 5,605,694; 5,225,183; 5,695,743; 5,439,670; and 6,352,684) is provided, and these patents are applicable to the product described in this application.

This NDA is being submitted in an electronic format and has been structured in compliance with the Agency's 1999 guidance document (*Guidance for Industry: Providing Regulatory Submissions in Electronic Format – NDAs*). This electronic submission is being provided on one DLT tape formatted using NT server 4.0 with NT backup. The size of this electronic submission is approximately 3 gigabytes.

Sepracor certifies that the data in this tape are free from viruses as determined by Network Associates VirusScanNT (version 4.5.1 SP1, using scan definition 4.0.4359 dated May 10, 2004).

The following table lists all the components of this eNDA and provides the file name or folder for each major NDA section.

Section No.	Section Title	Location
---	Cover Letter	*N21730\cover.pdf*
---	Form FDA 356h	*N21730\356h.pdf*
---	Reviewer's Guide	*N21730\guide.pdf*
1	Table of Contents (NDA Index)	*N21730\ndatoc.pdf*
2	Labeling	*N21730\labeling\ . . .*
3	Summary	*N21730\summary\summary.pdf*
4	Chemistry	*N21730\cmc\ . . .*
5	Nonclinical Pharmacology and Toxicology	*N21730\pharmtox\ . . .*
6	Human Pharmacology and Bioavailability / Bioequivalence	*N21730\hpbio\ . . .*
7	Clinical Microbiology	Not Applicable
8/10	Clinical Data / Statistical Section	*N21730\clinstat\ . . .*
9	Safety Update	Not Applicable
11	Case Report Tabulations	*N21730\crt\ . . .*
12	Case Report Forms	*N21730\crf\ . . .*
13	Patent Information	*N21730\other\patinfo.pdf*
14	Patent Certification	*N21730\other\patcert.pdf*
15	Establishment Description	Not Applicable
16	Debarment Certification	*N21730\other\debar.pdf*
17	Field Copy Certification	*N21730\other\fieldcer.pdf*
18	User Fee Cover Sheet (Form FDA 3397)	*N21730\other\userfee.pdf*
19	Financial Information	*N21730\other\financial.pdf*
20	Other: Regulatory History	*N21730\other\reghistory.pdf*

In accordance with the January 5, 2004, teleconference with the Division of Pulmonary and Allergy Drug Products, no paper desk copies or review copies of this NDA are being provided.

The only paper volume provided with this submission is an archival Volume 1, which contains the NDA Index (NDA Section 1, Table of Contents), the Reviewer's Guide, and the following original signed documents:

- Cover letter
- Form FDA 356h
- GLP Compliance Statement (from NDA Section 5, Nonclinical Pharmacology and Toxicology)
- GCP Compliance Statement (from NDA Section 8/10, Clinical Data / Statistical Section)
- Patent Information (NDA Section 13)
- Patent Certification (NDA Section 14)
- Debarment Certification (NDA Section 16)
- Field Copy Certification (NDA Section 17)
- User Fee – Form FDA 3397 (NDA Section 18)
- Financial Information (NDA Section 19)

In accordance with 21 CFR §314.50(l)(3) and 21 CFR §314.440(a)(4), and pursuant to the FDA Office of Regulatory Affairs notification to Docket 92S-0251 on September 24, 2003, Sepracor Inc. shall notify the District Office of the FDA that NDA 21-730 has been submitted. No field copy will be submitted, in accordance with the notification to Docket 92S-0251 referenced above.

The user fee number for this NDA 21-730 is 4738. Sepracor paid the user fee on March 18, 2004.

We greatly appreciate the guidance that has been provided to us by the Division of Pulmonary Drug Products during the development of this product, and we look forward to continued interactions with the Division to support your review of this application.

If you have questions regarding this submission please contact Ms. Renee Carroll by telephone at (508) 357-7598 or by fax at (508) 357-7491.

Sincerely,

Gautam Shah, Ph.D.
Senior Director, Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Sepracor Inc.	**May 11, 2004**
TELEPHONE NO. (Include Area Code) **(508) 357-7300**	FACSIMILE (FAX) Number (Include Area Code) **(508) 357-7491**
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* **84 Waterford Drive Marlborough, MA 01752-7010**	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* **21-730**

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
levalbuterol tartrate	**Xopenex HFA™**

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
(R)-α[1]-[[(1,1-dimethylethyl)amino]methyl]-4-hydroxy-1,3-benzenedimethanol L-tartrate (2:1 salt)

CODE NAME *(If any)* **N/A**

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
inhalation aerosol	**45 :g/actuation**	**oral inhalation**

(PROPOSED) INDICATION(S) FOR USE:
Treatment or prevention of bronchospasm in adults, adolescents, and children 4 years of age and older with reversible obstructive airway disease

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☒ 505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug	Holder of Approved Application
Proventil® Inhalation Solution (NDA 19-243)	**Schering Corporation**

TYPE OF SUBMISSION *(check one)* ☒ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Original New Drug Application

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☒ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See pages 3-4 for facility information. **All establishments listed in this application are ready for inspection.**

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

See pages 5-6 for application and DMF information.

This application contains the following items: *(Check all that apply)*		
☒	1. Index	**Electronic**
☒	2. Labeling *(check one)* ☒ Draft Labeling ☐ Final Printed Labeling	**Electronic**
☒	3. Summary (21 CFR 314.50(c))	**Electronic**
☒	4. Chemistry section	**Electronic**
☒	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)	**Electronic**
☐	B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
☒	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)	**Electronic**
☒	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)	**Electronic**
☒	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)	**Electronic**
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))	
☒	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)	**Electronic**
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)	
☒	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)	**Electronic**
☒	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)	**Electronic**
☒	12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)	**Electronic**
☒	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))	**Electronic & Paper**
☒	14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355(b)(2) or (j)(2)(A))	**Electronic & Paper**
☐	15. Establishment description (21 CFR Part 600, if applicable)	
☒	16. Debarment certification (FD&C Act 306(k)(1))	**Electronic & Paper**
☒	17. Field copy certification (21 CFR 314.50(k)(3))	**Electronic & Paper**
☒	18. User Fee Cover Sheet (Form FDA 3397)	**Electronic & Paper**
☒	19. Financial Information (21 CFR Part 54)	**Electronic & Paper**
☒	20. OTHER *(Specify)* **Regulatory History**	**Electronic**

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Gautam Shah, Ph.D. **Senior Director, Regulatory Affairs**	**May 11, 2004**

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
84 Waterford Drive, Marlborough, MA 01752-7010	**(508) 357-7710**

Public reporting burden for this collection of information is estimated to average 24 hours 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
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

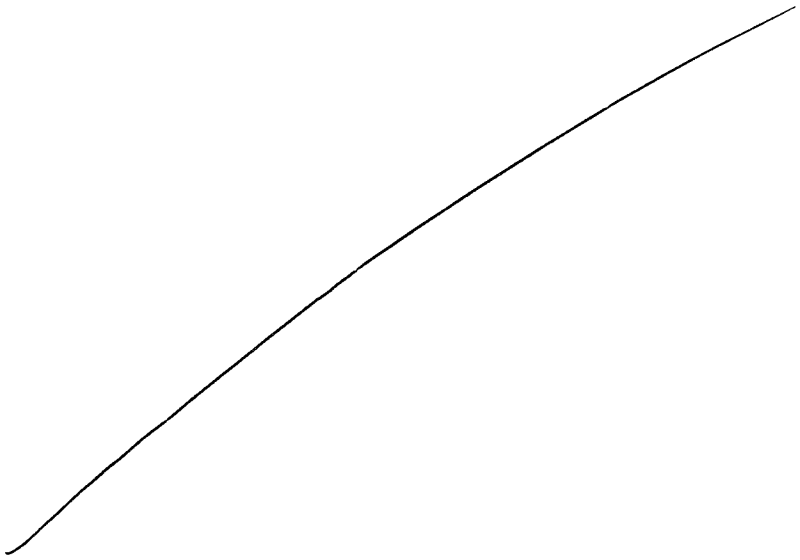
Food and Drug Administration
CDER, HFD-94
12420 Parklawn Dr., Room 3046
Rockville, MD 20852

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.

FORM FDA 356h (9/02)

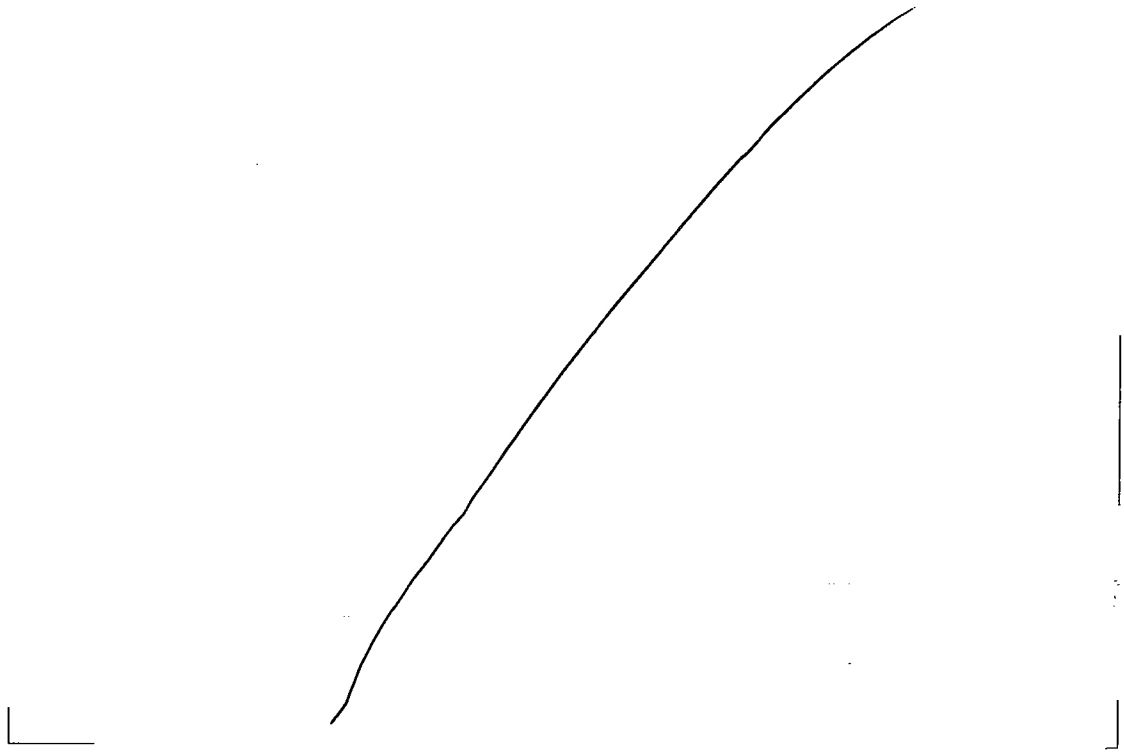
Locations of Manufacturing, Packaging, and Control Sites for Drug Substance

Establishment	Address and Telephone	Establishment Registration No.	Responsibility
Sepracor Canada Limited	P.O. Box 2880 24 Ivey Lane Windsor, Nova Scotia B0N 2T0 Canada 902-798-4100	3002808239	Chemical synthesis (R-benzyl albuterol and drug substance) Release and stability testing



Locations of Manufacturing, Packaging, and Control Sites for Drug Product

Establishment	Address and Telephone	Establishment Registration No.	Responsibility
3M Pharmaceuticals	19901 Nordhoff Street Northridge, CA 91324-3298 818-709-3014	CFI-2010441	Drug product manufacture and packaging Release and stability testing



List of Related INDs and NDAs

Application	Application Number	Product
U.S. IND	IND 62,906	Xopenex HFA™ (levalbuterol tartrate HFA) Inhalation Aerosol
U.S. IND	IND 47,363	Xopenex® (levalbuterol HCl) Inhalation Solution
U.S. NDA	NDA 20-837	Xopenex® (levalbuterol HCl) Inhalation Solution
U.S. NDA	NDA 19-243	Proventil® Inhalation Solution
U.S. NDA	NDA 20-503	Proventil® HFA Inhalation Aerosol

f

1 Page(s) Withheld

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

_ § 552(b)(5) Deliberative Process

_ § 552(b)(4) Draft Labeling

User Fee Cover Sheet

This section provides the User Fee Cover Sheet (Form FDA 3397) and a copy of the check that was submitted on March 18, 2004, as payment of the user fee for this application.

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: December 31, 2006.

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/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Sepracor Inc.
84 Waterford Drive
Marlborough, MA 01752-7010

2. TELEPHONE NUMBER *(Include Area Code)*

(508) 357-7710

3. PRODUCT NAME

Xopenex HFA™ (levalbuterol tartrate HFA) Inhalation Aerosol

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

N021730

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).

6. USER FEE I.D. NUMBER

4738

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 SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(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
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

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	TITLE	DATE
[signature]	Senior Director, Regulatory Affairs	03/18/2004

FORM FDA 3397 (12/03)

PSC Media Arts (301) 443-1090 EF

SEPRACOR

REMITTANCE ADVICE

R&D A/P ACCOUNT
84 WATERFORD DRIVE
MARLBOROUGH, MA 01752

Check No. 30017

Date : 18-MAR-04 Vendor Name : FOOD AND DRUG ADMINIST Vendor No. : FOODR

FEE ID 4738 NDA 21-730	11-MAR-04		0.00	573,500.00
			0.00	573,500.00

SEPRACOR INC.
R&D A/P ACCOUNT
84 WATERFORD DRIVE
MARLBOROUGH, MA 01752

Check No. 30017

52-160
112

CHECK DATE	CHECK AMOUNT
18-MAR-04	$ 573,500.00

Five Hundred Seventy-Three Thousand Five Hundred Dollars And 00 Cents

PAY TO THE ORDER OF
FOOD AND DRUG ADMINISTRATION
PO BOX 360909
PITTSBURGH, PA 15251-6909
United States

AUTHORIZED SIGNATURE

Fleet Maine, N.A.
South Portland, ME

VOID AFTER 180 DAYS

⑈30017⑈ ⑆011201538⑆ 00802 18084⑈

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

FACSIMILE TRANSMITTAL SHEET

Date: January 21, 2004

To: Gautam Shah, Ph.D. **Senior Director, Regulatory Affairs**	**From:** Akilah Green Regulatory Project Manager
Company: Sepracor	Division of Pulmonary and Allergy Drug Products
Fax number: 508-357-7491	**Fax number:** 301-827-1271
Phone number: 508-357-7710	**Phone number:** 301-827-5585

Subject: IND 62,906 January 5, 2004, meeting minutes

Total no. of pages including cover: 6

Comments:

Document to be mailed: YES XNO

Memorandum of Telephone Facsimile Correspondence

Date: January 21, 2004

To: Gautam Shah, Ph.D.
Senior Director, Regulatory Affairs

Fax: 508-357-7491

From: Akilah Green
Regulatory Project Manager

Subject: IND 62,906/Xopenex HFA MDI
January 5, 2004, meeting minutes

Reference is made to the meeting held between representatives of your company and this Division on January 5, 2004. Attached is a copy of our final minutes for that meeting. These minutes will serve as the official record of the meeting. If you have any questions or comments regarding the minutes, please call me at (301) 827-5585.

Thank you.

Memorandum of Teleconference

Date: January 5, 2004

Time: 1:00 – 2:00pm

Application: IND 62,906/ Xopenex HFA MDI/Sepracor
PreNDA CMC Meeting

Between:

Name: David Amato, Ph.D., Sr. Director, Biostatistics
Rudolf Baumgartner, M.D., Vice President, Clinical Research
Donna Grogan, M.D., Sr. Vice President, Clinical Research
William McVicar, Ph.D., Executive Program Director, Product Development
Marcel Moulaison, Associate Director, Technical Quality Assurance
Stewart Mueller, Sr. Vice President, Regulatory Affairs and Quality
Gautam Shah, Ph.D., Sr. Director, Regulatory Affairs
Phone: 1-508-357-7765
Representing: Sepracor

AND:

Name: Badrul Chowdhury, M.D., Ph.D., Division Director
Eugene Sullivan, M.D., Deputy Director
Richard Nicklas, M.D., Clinical Reviewer
Emmanuel Fadiran, Ph.D., Clinical Pharmacology and Biopharmaceutics Team Leader
Lori Garcia, Regulatory Project Manager
Akilah Green, Regulatory Project Manager
Division of Pulmonary and Allergy Drug Products, HFD-570

SUBJECT: To discuss Sepracor's plan to assess MDI device compliance in ongoing Study 051-356, as propose in the meeting request and briefing package dated December 5, 2003.

The Division addressed the following questions, in bold italics.

Question 1

Does the Division concur with our plan to test at least 100 non-compliant samples (representing devices used prior to implementation of the protocol amendment submitted via Serial No. 095) and to test for microbiological data using — — each, as described in Part A of the device reliability assessment plan?

The Division agreed with the plan to test at least 100 non-complaint samples and the plan for microbiological assessment; however, the Division disagreed with Sepracor's proposal to evaluate devices that have been used for as little as approximately 4 days (i.e.

25 actuations). Patients will take 2 puffs of Xopenex qid. This would be 8 puffs per day or 24 puffs in 3 days. Sepracor is proposing to accept for analysis canisters that contains 175 actuations or less (25 actuations or more would have been used). The Division has consistently asked sponsors to study devices that have been used by patients, as close to the end of the device life as possible (recognizing the need to have some drug left for in-vitro testing). Sepracor stated that they have conducted a random sample of their store of MDIs that were used in prior clinical trials. This random sample suggested that very few of the stored MDIs are near the end of their lives. For instance, only 13% of the devices sampled had between 35 and 50 actuations left in the canister. Sepracor stated that 35 actuations was the minimum number of actuations necessary to perform in-vitro analysis. The Division stated that Sepracor should evaluate at least 100 devices that have 35-50 actuations remaining.

Question 2

Does the Division concur that the approach described in Part B of the plan will provide data adequate in scope (i.e., comparable to what might have been obtained from the two Phase III studies in adults) so as to permit assessment of device performance in the levalbuterol MDI NDA?

The Division noted that the computations made by the sponsor in order to estimate the exposure that occurred in the two 8 week phase 3 studies with this drug product are not ideal. The computations are based on the number of patients who completed 8 weeks of treatment in the two 8 week studies. They do not include 53 patients who were randomized but did not complete these studies, and they do not include patients from the long-term safety study. The Division stated that device performance data are customarily generated from the entire Phase 3 program. Therefore, the proposed 800 subject can-cycles represents less data than would typically be expected. The Division stated that the adequacy of the database will be a review issue, and that Sepracor should submit as much data as it can. The Division emphasized that device performance is particularly critical in a product that is to be used as rescue medication for patients with asthma.

Question 3

Does the Division concur with the diary card and call-center-administered questionnaire approach to screening for complaint samples, as described in Part C of the plan?

The Division stated that this seems to be a reasonable approach and consistent with the Division's recommendations. The Division asked for clarification from Sepracor about the type of in-vitro testing that would be done on complaint devices, since on page 6 of the briefing document it states that the call center questionnaire "information will guide the appropriate testing of the devices in accordance with the reported difficulty". Sepracor responded that all devices would undergo the extensive in-vitro testing as outlined on page 8 of the briefing document, but that, in addition, complaint devices might have more extensive evaluation based on the type of complaint.

Question 4

Does the Division concur with the proposal for submission of device performance data that we have outlined in Part D of the plan?

The Division requested that Sepracor clarify what they are proposing to submit with the NDA and with the 120-day safety report, and when the ongoing 12-month safety study will end. Sepracor stated that they plan to include the entire data analysis on the 100 non-complaint devices and patient diary reports on approximately 200 of the 800 study patient can cycles in the NDA submission. Results of the *in vitro* testing on any complaint devices might not be available at the time of NDA submission. All of the device performance data will be submitted either with the NDA or with the 120 day safety update, including the balance of the study patient can cycles not submitted at the time of NDA submission. Sepracor anticipates that study 356 will run throughout 2004 and that the NDA will be submitted in the first quarter of 2004. The Division emphasized the importance of device performance data, and stated that the original NDA submission should contain a database that is adequate to support the performance of the device. In this telephone conference and in prior meetings, the Division has conveyed the typical device performance database that is expected. If the entire device performance database is not submitted with the NDA, whether the data submitted is adequate to support the approval of the drug product will become a review issue. Sepracor stated that they understand the Division's stance, and that they are confident that they will be able to adequately demonstrate device performance.

The Division noted that Sepracor plans to instruct patients on cleaning the device. The Division asked if Sepracor plans to use the same instructions in the labeling. Sepracor confirmed that they plan to use the same instructions in the labeling. Their rationale for providing detailed instructions was that the racemic MDI comparator product being used in the same study has detailed instructions.

The Division informed Sepracor that the statistical analysis of the data in regard to device performance that they proposed is not appropriate. The incidence of device malfunction should be the sum of all of the devices that malfunction on in-vitro testing, (whether or not the malfunction is detected by the patient), divided by the number of devices used by patients in the study. Note that the most appropriate denominator is the number of devices, not the number of doses. In addition, the Division stated that the overall judgement regarding the acceptability of device performance will be based on the data as a whole, not simply the incidence calculation.

_____

Akilah Green
Regulatory Project Manager

cc:

HFD-570/Division Files
HFD-570/Chowdhury
HFD-570/Sullivan
HFD-570/Nicklas
HFD-570/Fadiran

Drafted by:	A. Green/January 13, 2003
Initialed:	Sullivan/January 15, 2003
	Nicklas/January 14, 2004
	Chowdhury/January 20, 2004
Finalized:	A. Green/January 21, 2004

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

FACSIMILE TRANSMITTAL SHEET

Date: November 14, 2003

To: Guatam Shah, Ph.D. **Senior Director, Regulatory Affairs**	**From:** Akilah Green Regulatory Project Manager
Company: Sepracor	Division of Pulmonary and Allergy Drug Products
Fax number: 508-357-7491	**Fax number:** 301-827-1271
Phone number: 508-357-7710	**Phone number:** 301-827-5585

Subject: IND 62,906 October 29, 2003, meeting minutes

Total no. of pages including cover: 16

Comments:

Document to be mailed: YES XNO

Memorandum of Telephone Facsimile Correspondence

Date: November 14, 2003

To: Guatam Shah, Ph.D.
Senior Director, Regulatory Affairs

Fax: 508-357-7491

From: Akilah Green
Regulatory Project Manager

Subject: IND 62,906/ Xopenex HFA MDI/Sepracor
October 29, 2003, meeting minutes

Reference is made to the meeting held between representatives of your company and this Division on October 29, 2003. Attached is a copy of our final minutes for that meeting. These minutes will serve as the official record of the meeting. If you have any questions or comments regarding the minutes, please call me at (301) 827-5580.

Thank you.

Memorandum of Meeting Minutes

Meeting Date: October 29, 2003

Time: 3:00 – 4:30pm

Location: Food and Drug Administration/Parklawn Building
17th Floor, Conference Room 05

Application: IND 62,906/ Xopenex HFA MDI/Sepracor

Sepracor Representatives:

David Amator, Ph.D., Senior Director, Biostatistics
Timothy Barberich, Chairman and CEO, Sepracor
Rudolf Baumgartner, M.D., Vice President, Clinical Research
Mark Corrigan, M.D., Executive Vice-President, Research and Development
Donna Grogan, M.D., Senior Vice-President, Clinical Research
John Hanrahan, M.D., Senior Medical Director, Clinical Research
Gary Maier, Ph.D., Executive Director, Clinical Pharmacology
William Vicar, Ph.D., Executive Program Director, Product Development
Gautum Shah, Ph.D., Senior Director, Regulatory Affairs
Kenneth Tripp, Associate Director, Biostatistics
James Wachholz, Executive Director, Regulatory Affairs

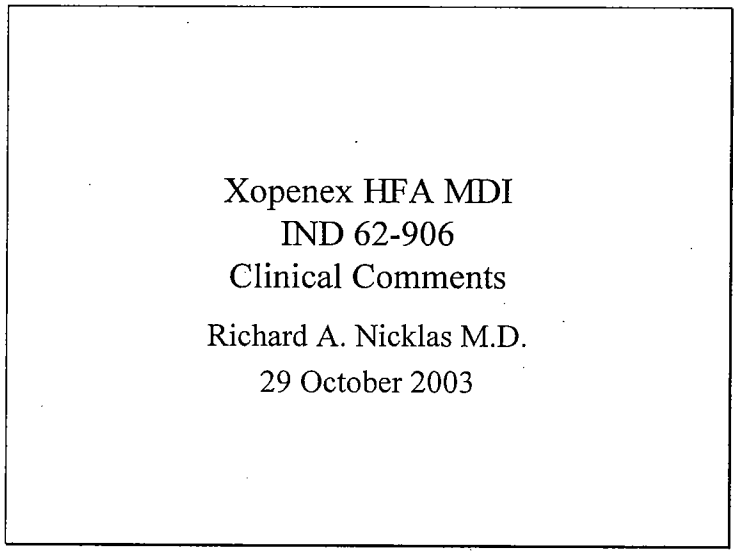
Division of Pulmonary and Allergy Drug Products (DPADP) Representatives:

Badrul A. Chowdhury, M.D., Ph.D., Division Director
Eugene Sullivan, M.D., Acting Clinical Team Leader
Richard Nicklas, M.D., Clinical Reviewer
Sandra Suarez, Ph.D., Clinical Pharmacology and Biopharmaceutics Reviewer
Jim Gebert, Ph.D., Acting Statistics Team Leader
Feng Zhou, M.S., Statistics Reviewer
Akilah Green, Regulatory Project Manager

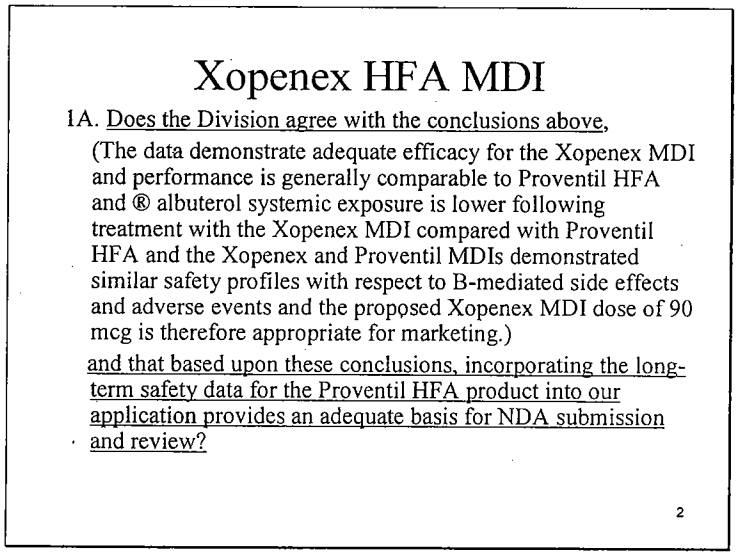
Subject: Sepracor submitted a meeting request dated July 21, 2003, to discuss their Phase II and Phase III data and clinical development program. The meeting package was received on October 1, 2003.

Discussion:

Slide 1



Slide 2



Slide 3

Xopenex HFA MDI

- 1A. Division's Response
  - We can not say whether we agree with your conclusions until we have had the opportunity to review the entire database that supports those conclusions.
  - The program as described appears adequate for NDA submission and review.
  - Incorporating the long-term safety data from the Proventil HFA MDI, in conjunction with the other safety and efficacy data that has been generated does provide an adequate basis for NDA submission and review.
  - The 12 month safety study should be submitted at the time of the original submission if you feel that the data are necessary in order to adequately define the safety of this drug product.

3

Slide 4

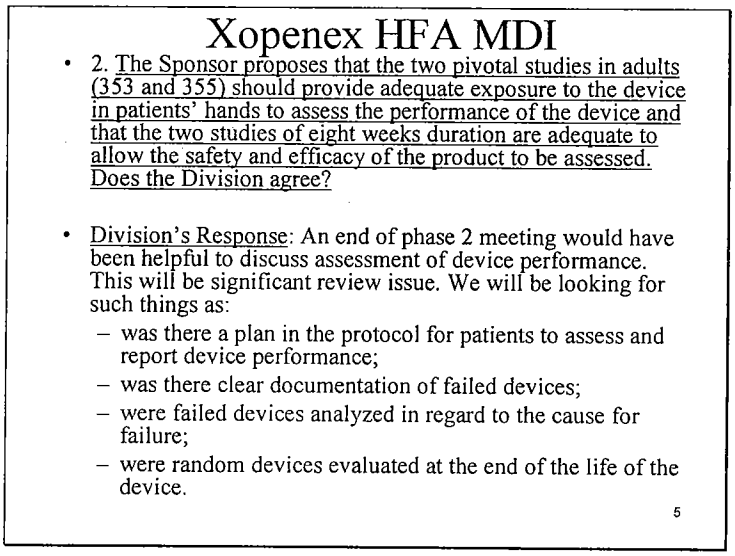
Xopenex MDI HFA

- 1B. Based on the efficacy and safety data in adults, the pediatric studies to be included in this file, and the availability of pharmacokinetic data describing the relationship between the PK in adults and children, does the Division concur that there will be adequate information in the NDA to support a review and decision regarding a pediatric indication?

- Division's response: Yes.

4

Slide 5

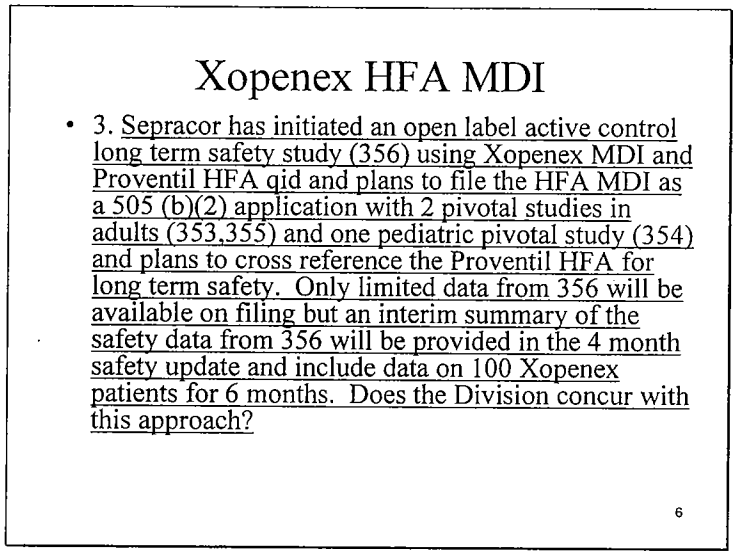


The Division questioned whether or not Sepracor had acceptable data on device performance. The Division stated that it customarily expects that the pivotal clinical trials include diary questions related to device performance, collection and analysis of any devices reported to be possibly malfunctioning ("complaint devices"), and collection and analysis of a certain number of devices that apparently functioned normally ("non-complaint devices"). Sepracor stated that, although they did not specifically invite patients to report on device problems, they could provide data on the number of spontaneous reports of device problems. In addition, Sepracor stated that the protocols did specify that patients use their own devices during clinic visits, and that this may provide some evidence of device performance. Sepracor also stated that they may be able to perform *in vitro* testing on devices that were returned at the end of the study, which are still in storage. The Division suggested that Sepracor consider modifying its

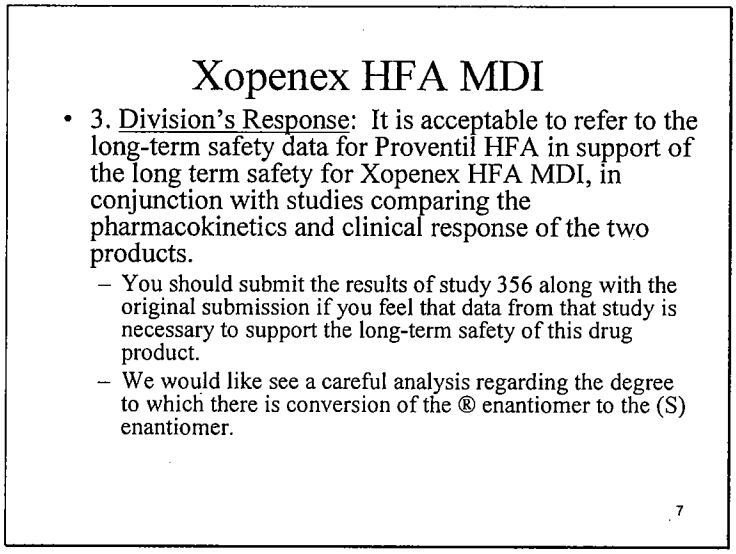
ongoing clinical study to prospectively acquire device performance data. The Division reminded Sepracor that device performance is vital and that Sepracor will not receive an NDA approval without adequate data about the performance of the device. Although in-vitro data is helpful, the Division believes that device performance must also be investigated in the clinical setting. Sepracor does not appear to have adequate data on the device performance at the end of the canister life.

Sepracor asked if they could provide information on device performance at the safety update. The Division indicated that the application must be complete at the time of submission. Therefore, any information used to establish device performance must come in at the time of the initial submission. If the data is submitted later, there may not be a chance to review it during the review cycle. Sepracor is taking a substantial risk if they submit an NDA for this drug product without device performance data.

Slide 6



Slide 7



Sepracor questioned if the Division was referring to conversion of the (R) to the (S) enantiomer in the can or in the body. The Division responded that we are looking for data on conversion in the body. Sepracor asked if, based on the information submitted in the background package, the Division felt the data from Study 356 would be necessary. The Division stated that if, after Sepracor reviews their safety database, they feel the data from Study 356 is needed, then they should submit it at the time that they submit the NDA. The Division saw no safety signal based on the summary data provided to us that would indicate that the 12 month safety data definitely needs to be submitted.

Slide 8

End-of-Phase II Meeting
Xoponex HFA MDI

Sepracor

CLINICAL PHARMACOLOGY COMMENTS

October 29, 2003

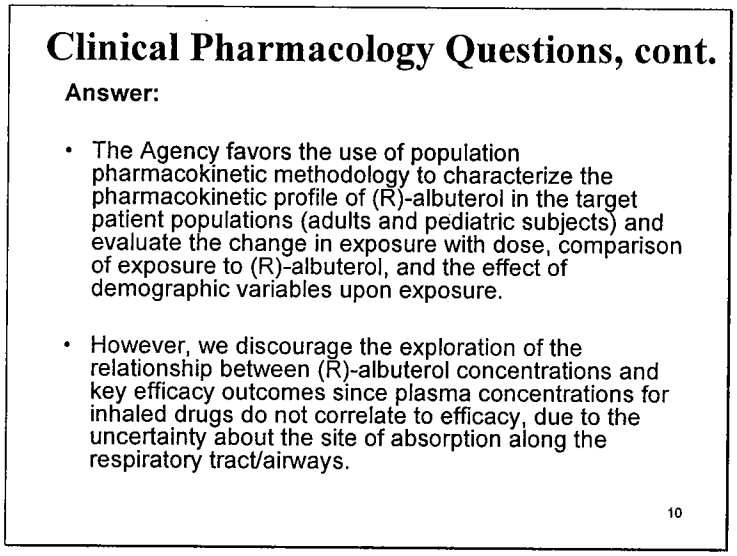
Slide 9

Clinical Pharmacology Questions

- Question 4. Sepracor intends to use population pharmacokinetic methodology to characterize the pharmacokinetic profile of (R)-albuterol in the target patient populations (adults and pediatric subjects) and evaluate the change in exposure with dose, comparison of exposure to (R)-albuterol, and the effect of demographic variables upon exposure, and will characterize the relationship between exposure to (R)-albuterol and percent change in FEV1.

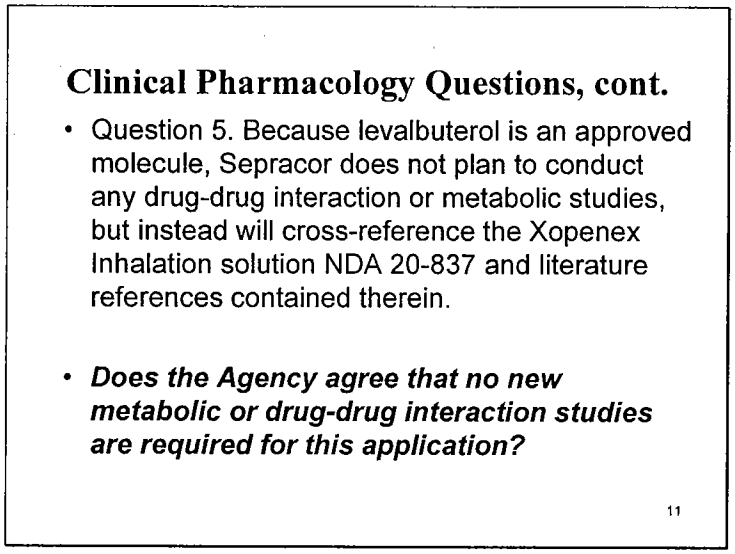
- ***Does the Agency agree that the approach as outlined will provide adequate information to support NDA review and that no additional pharmacokinetic studies are required either in the adult or pediatric populations?***

Slide 10

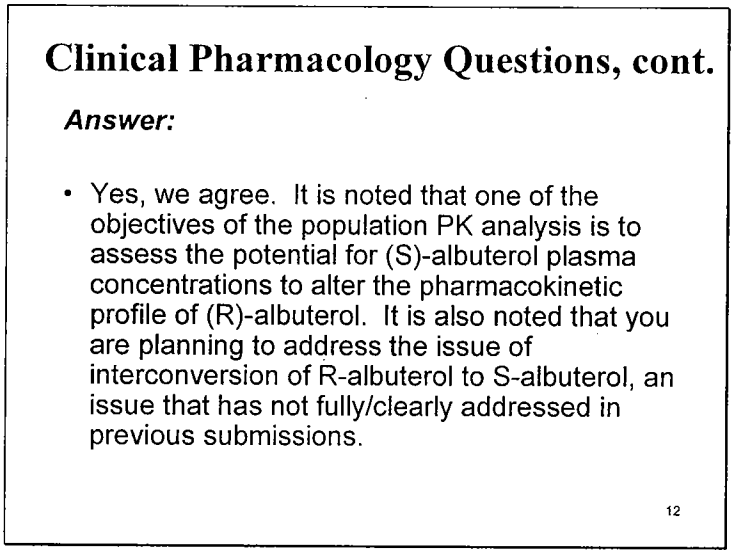


Sepracor asked if the reason for not recommending the exploration of a relationship between R-albuterol and key efficacy outcomes was related to the time spent to review the data. The Agency replied by saying that the main reason was well known and that was because plasma concentrations do not represent the drug concentration at the site of action. The Agency added that following inhalation, plasma concentrations are the results of GI absorption and absorption along the airways which may not necessarily correspond to the site of action. The sponsor replied that the oral BA of the drug was very low due to a high first pass effect. The Agency added that independently of that the above mentioned stills holds true.

Slide 11



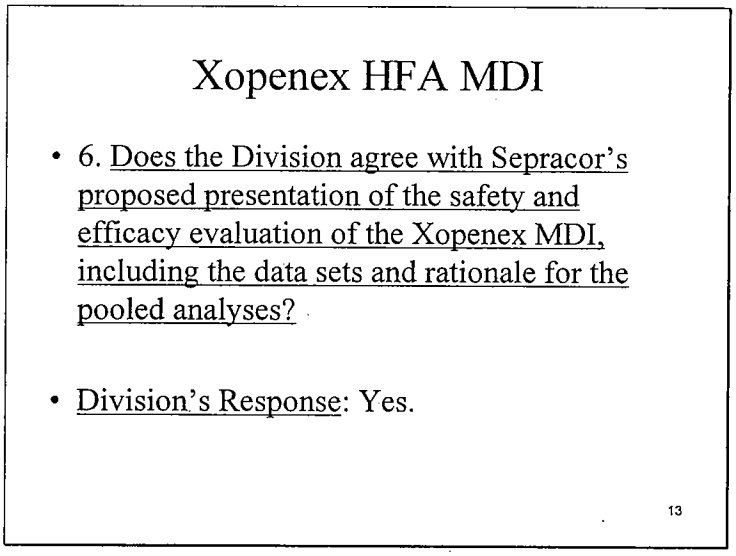
Slide 12



Sepracor requested assistance on the type of analysis they could use to address the issue of interconversion. The Division was unable to provide any example during the meeting, but agreed to provide some examples if available as an addendum to the meeting minutes. Sepracor noted that in the UDV for any product more than a week old there is some (S) albuterol. Therefore, it appeared that the conversion was happening in vitro. The

Division stated that independent of the place of interconversion, the sponsor should characterize the extent of it. The sponsor inquired that if they were no seeking for an interconversion claim would they needed to address this issue. The Agency replied that if there were not safety and efficacy implications then they did not need to address the issue of interconversion. The Agency added that in the clinical trials conducted in adults to compare proventil vs. levalbuterol, the systemic exposure of (S)-albuterol following raceminc albuterol administration was much higher than that for the R-albuterol. The Agency added that the sponsor needed to explain this observation. They also indicated that they submitted ISS, TOC, and structure, where they reevaluated the CFC studies. The safety evaluation did not add sufficient information to include it. The Division stated that Sepracor does not have to include it as long as they have the data from the studies.

Slide 13



Slide 14

Xopenex HFA MDI

- 7. Does the Division agree that our proposal to omit patient profile listings in the electronic NDA submission is acceptable?
- Division's Response: Yes, however patient profiles for all serious and severe adverse events and deaths should be included in the submission.

14

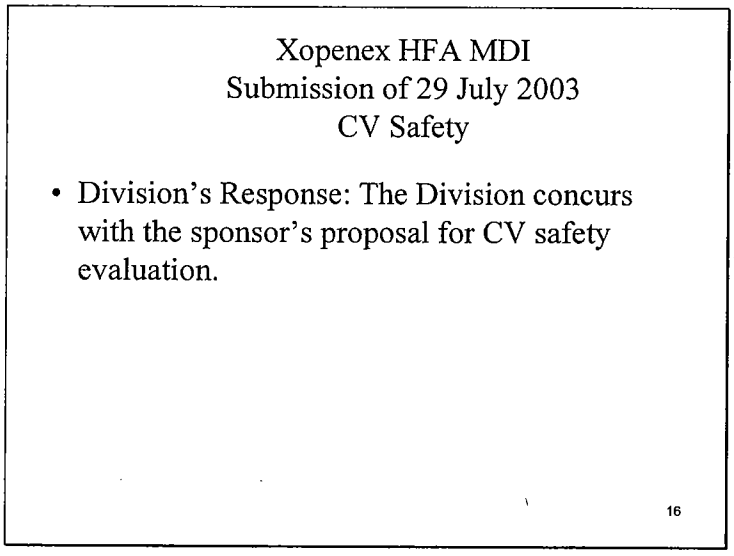
Slide 15

Xopenex HFA MDI
Submission of 29 July 2003
CV Safety

- Does the Agency concur with Sepracor's proposal for cardiovascular safety evaluation for the NDA?
  - Reference to Xopenex Inhalation Solution for 6 years of age and older – NDA and post-marketing
  - Reference to Proventil HFA MDI for long term safety in adults
  - Reference to Ventolin MDI for non-clinical safety data

15

Slide 16



Post presentation discussion:

Sepracor questioned whether the Division felt that the proposed Xopenex MDI dose of 90 mcg is appropriate for marketing. The Division indicated that Sepracor's dose selection appears appropriate

Sepracor stated that they intend to submit dose-counter information as part of an amendment to the NDA and questioned if it the dose-counter data would sufficiently address the overall device performance. The Division advised that attempts to establish overall device performance and dose-counter performance in the same study may introduce unnecessary complexity. Also, device performance data should be submitted with the original submission. Sepracor asked if there was any value in retrospectively asking patients questions about device failures. The Division stated that such an approach is problematic. Patients recall may not be accurate, and the Sepracor will be unable to find specific devices that may have malfunctioned in order to test them. .

Sepracor asked how many apparently normally functioning devices from clinical trials should be tested, and how many patients should be followed prospectively for reports of device problems. The Division stated that it would discuss the number of devices internally, and include a recommendation in a post-meeting addendum (see below). In regard to the number of patients followed prospectively, the Division stated that it usually expects that all of the patients in the Phase 3 program will be asked prospectively to record any perceived problems with the device, and that any devices reported as possibly malfunctioning be collected and analyzed.

Post-Meeting Addendum

After internal discussion and consideration, the Division has the following advice regarding the number of non-complaint devices (i.e. those that were used in clinical trials and apparently functioned normally) that should be collected and analyzed for *in vitro* characteristics. The characteristics that should be studied include appearance, delivered dose uniformity, aerodynamic particle size, microscopic evaluation of content, microbial load, and [redacted] The number of non-complaint devices that should be analyzed generally varies with the complexity of the device, as well as the number and nature of complaint devices from the clinical trials. In regard to the Xopenex HFA product, at least 100 non-complaint devices should be analyzed. If these analyses suggest a particular potential problem with device performance at the end of the life of the device, further data may be necessary.

Akilah Green
Regulatory Project Manager

cc:

HFD-570/Division Files
HFD-570/Chowdhury
HFD-570/Sullivan
HFD-570/Nicklas
HFD-570/Suarez
HFD-570/Gebert
HFD-570/Zhou

Drafted by: A. Green/November 3, 2003
Initialed: Nicklas/November 3, 2003
Sullivan/November 4, 2003
Suarez/November 6, 2003
Chowdhury/November 12, 2003
Finalized: A. Green/November 14, 2003

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

FACSIMILE TRANSMITTAL SHEET

Date: October 21, 2003

To: Cheryl Larrivee-Elkins **Associate Director, Technical** **Regulatory Affairs**	**From:** Akilah Green Regulatory Project Manager
Company: Sepracor	Division of Pulmonary and Allergy Drug Products
Fax number: 508-357-7491	**Fax number:** 301-827-1271
Phone number: 508-357-7871	**Phone number:** 301-827-5580

Subject: IND 62,906 September 30, 2003, PreNDA meeting minutes

Total no. of pages including cover: 13

Comments:

Document to be mailed: YES XNO

Memorandum of Telephone Facsimile Correspondence

Date: October 21, 2003

To: Cheryl Larrivee-Elkins
Associate Director, Technical Regulatory Affairs

Fax: 508-357-7491

From: Akilah Green
Regulatory Project Manager

Subject: IND —
September 30, 2003, meeting minutes

Reference is made to the meeting held between representatives of your company and this Division on September 30, 2003. Attached is a copy of our final minutes for that meeting. These minutes will serve as the official record of the meeting. If you have any questions or comments regarding the minutes, please call me at (301) 827-5580.

Thank you.

Memorandum of Meeting Minutes

Meeting Date: September 30, 2003

Time: 2:30 – 4:00pm

Location: Food and Drug Administration/Parklawn Building
17th Floor, Conference Room 05

Application: IND 62,906/ Xopenex HFA MDI/Sepracor
PreNDA CMC Meeting

Sepracor Representatives:

Rudy Baumgartner, M.D., Vice President, Medical Operations
Alex Jurgens, Ph.D., Executive Director, Technical Services and Quality Control
Cheryl Arrive-Elkins, Associate Director, Technical Regulatory Affairs
Paul McGlynn, Ph.D., Director, Aerosol Development
William McVicar, Ph.D., Executive Program Director
Marçel Moulaison, Associate Director, Technical Quality Affairs
Stud Mueller, Senior Vice President, Regulatory Affairs and Quality
Prabu Nambiar, Ph.D., Director, Technical Regulatory Affairs
Pat Noland, Director, Quality Operations
Gautum Shah, Ph.D., Senior Director, Regulatory Affairs
Stephen Wald, Senior Vice President, Chemical Research and Development

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

Guirag Poochikian, Ph.D., Chemistry Team Leader
Craig Bertha, Ph.D., Chemistry Reviewer
Ted Guo, Ph.D., Statistical Reviewer
Akilah Green, Regulatory Project Manager

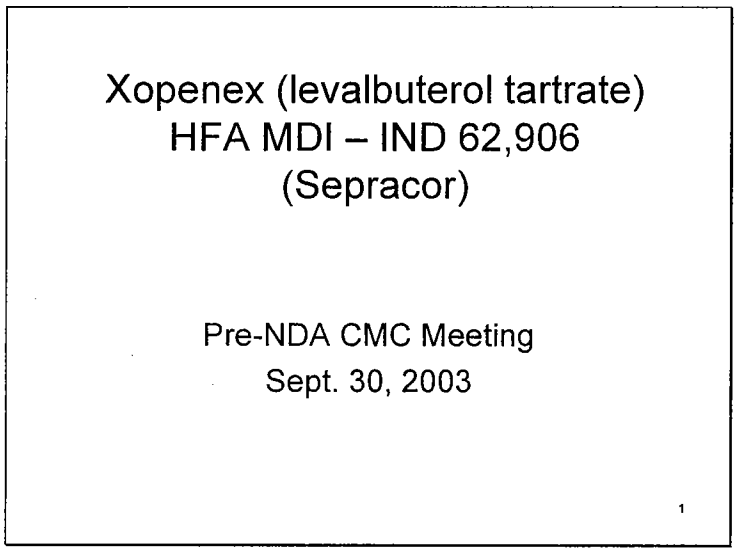
Office of Pharmaceutical Science

Eric Duffy, Ph.D., Director, Division of New Drug Chemistry II

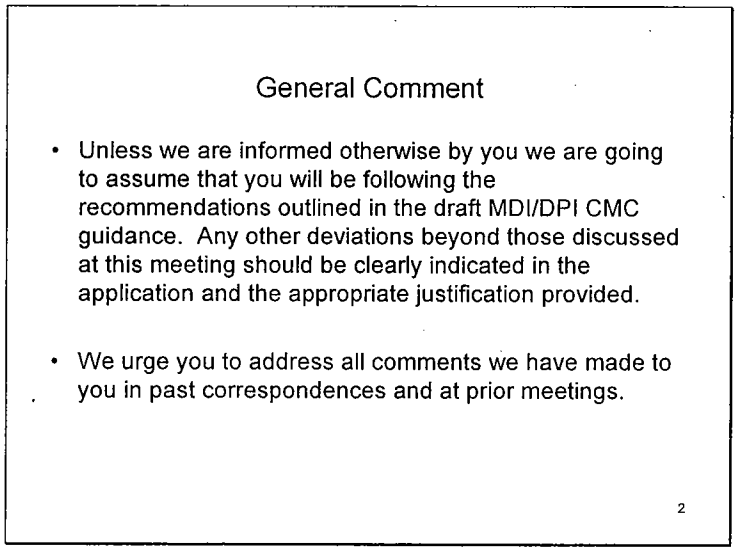
Subject: To discuss the Chemistry, Manufacturing, and Controls portion of the eNDA Sepracor plans to pre-submit.

Discussion:

Slide 1



Slide 2



Slide 3

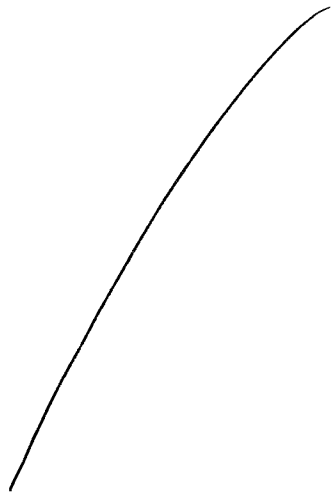
1. Does the Division have any comments or requests regarding the proposed [table of] contents of the CMC sections of the Xopenex HFA NDA as outlined in this pre-meeting information package (see appendix C)?

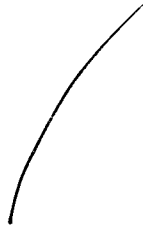
- We recommend that you make reference to the categories covered in the recent ICH guidance on the CTD format to assure that no key sections have been left out, e.g., discussion of overages.

APPEARS THIS WAY
ON ORIGINAL

3

Slide 4





9

7 Page(s) Withheld

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

_ § 552(b)(5) Deliberative Process

_ § 552(b)(4) Draft Labeling

cc:

HFD-570/Division Files
HFD-570/Poochikian
HFD-570/Bertha
HFD-570/Guo
HFD- /Duffy

Drafted by: A. Green/October 14, 2003
Initialed: Bertha/October 15, 2003
Poochikian/October 15, 2003
Finalized: A. Green/October 21, 2003