CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-837

# MICROBIOLOGY REVIEW(S)

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JAN 2 9 1999

**REVIEW FOR HFD-570**

**OFFICE OF NEW DRUG CHEMISTRY**
**MICROBIOLOGY STAFF HFD-805**
**Microbiologist's Review #3 of NDA 20-837**
**January 22, 1999**

A. 1. **APPLICATION NUMBER:** 20-837

**APPLICANT:** Sepracor Inc.
111 Locke Drive
Marlborough, MA 01752
(508) 481-7683

2. **PRODUCT NAME:** Xopenex™ Inhalation Solution

3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:** Sterile levalbuterol HCl inhalation solution ( 0.63 mg, and 1.25 mg) packaged in unit dose 3 mL LDPE vials. Administration via nebulization.

4. **METHODS OF STERILIZATION:**

5. **PHARMALOGICAL CATAGORY and/or PRINCIPLE INDICATION:** Beta$_2$-adrenergic receptor antagonist indicated for the treatment or prevention of bronchospasm.

6. **DRUG PRIORITY CLASSIFICATION:** P

B. 1. **DATE OF INITIAL SUBMISSION:** 7/30/97

2. **DATE OF AMENDMENTS:** *5/28/98* **8/6/98**

3. **DATE OF CONSULT:** 2/10/98 *6/10/98* **11/3/98**

4. **ASSIGNED FOR REVIEW:** 2/18/98 *6/11/98* **11/17/98**

C. **REMARKS:** Microbiologist's Review #1 yielded three deficiencies which were conveyed (via an IR letter) to the applicant on May 20, 1998. Microbiologist's Review #2 yielded one deficiency (pertaining to from the May 28, 1998 amendment. The applicant's response (8/6/98 amendment) to the deficiency is the subject of this review (Microbiologist's Review #3).

## D. CONCLUSIONS:

The submission is recommended for approval for issues concerning sterility assurance.

/S/ 1/22/99
Neal Sweeney, Ph.D.
/S/ 1/24/99

cc: NDA 20-837
HFD-570/Division File
HFD-570/CSO/P. Jani
HFD-570/Chemist/V. Shah
HFD-805/Consult File/N. Sweeney

Drafted by: N. Sweeney, January 22, 1999
R/D initialed by P. Cooney, January 22, 1999

APPEARS THIS WAY
ON ORIGINAL

JUN 16 1998

**REVIEW FOR HFD-570**

**OFFICE OF NEW DRUG CHEMISTRY**
**MICROBIOLOGY STAFF HFD-805**
**Microbiologist's Review #2 of NDA 20-837**
**June 16, 1998**

A. 1. **APPLICATION NUMBER:** 20-837

**APPLICANT:** Sepracor Inc.
111 Locke Drive
Marlborough, MA 01752
(508) 481-7683

2. **PRODUCT NAME:** [redacted] Inhalation Solution

3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:** Sterile levalbuterol HCl inhalation solution [redacted] 0.63 mg, and 1.25 mg) packaged in unit dose [redacted] 3 mL LDPE bottles. Administration via nebulization.

4. **METHODS OF STERILIZATION:** [redacted]

5. **PHARMALOGICAL CATAGORY and/or PRINCIPLE INDICATION:** $Beta_2$-adrenergic receptor antagonist indicated for the treatment or prevention of [redacted] bronchospasm.

6. **DRUG PRIORITY CLASSIFICATION:** P

B. 1. **DATE OF INITIAL SUBMISSION:** 7/30/97

2. **RELATED DOCUMENTS:** (none)

3. **DATE OF AMENDMENT:** *5/28/98*

4. **DATE OF CONSULT:** 2/10/98 *6/10/98*

5. **ASSIGNED FOR REVIEW:** 2/18/98 *6/11/98*

C. **REMARKS:** Microbiologist's Review #1 yielded three deficiencies which were conveyed (via an IR letter) to the applicant on May 20, 1998. The applicant's response is the subject of this review, Microbiologist's Review #2.

## D. CONCLUSIONS:

The submission is approvable pending resolution of container/closure issues.

/S/ 6/16/98
Neal Sweeney, Ph.D.
/S/ 6/16/98

cc: NDA 20-837
HFD-570/Division File
HFD-570/CSO/P. Jani
HFD-570/Chemist/V. Shah
HFD-805/Consult File/N. Sweeney

Drafted by: N. Sweeney, June 16, 1998
R/D initialed by P. Cooney, June 16, 1998

APPEARS THIS WAY
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pages of trade

secret and/or

confidential

commercial

information

| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>PUBLIC HEALTH SERVICE<br>FOOD AND DRUG ADMINISTRATION | | | **REQUEST FOR CONSULTATION** /S/ 2-11-98 | |
|---|---|---|---|---|
| *(Division/Office)*<br>Supervisory Microbiologist HFD-160 | | | FROM:<br>Vibhakar J. Shah (HFD-820) | |
| DATE<br>February 10, 1998 | IND NO. | NDA NO.<br>20837 | TYPE OF DOCUMENT<br>Original Application | DATE OF DOCUMENT<br>July 30, 1997 |
| NAME OF DRUG<br>Levalbuterol•HCl Inhalation Solution | | PRIORITY CONSIDERATION<br>3 | CLASSIFICATION OF DRUG<br>S | DESIRED COMPLETION DATE<br>4-11-98<br>Driving date 6-1-98 |
| NAME OF FIRM<br>Sepracor Inc. 111, Locke Drive, Marlborough, MA 01752; Tel: (508) 481 -6700 Fax: (508) 481-7683 | | | | |

/S/ 2/11/98

**REASON FOR REQUEST**

**I. GENERAL**

| | | |
|---|---|---|
| ☐ NEW PROTOCOL | ☐ PRE-NDA MEETING | ☐ RESPONSE TO DEFICIENCY LETTER |
| ☐ PROGRESS REPORT | ☐ END OF PHASE II MEETING | ☐ FINAL PRINTED LABELING |
| ☐ NEW CORRESPONDENCE | ☐ RESUBMISSION | ☐ LABELING REVISION |
| ☐ DRUG ADVERTISING | ☐ SAFETY/EFFICACY | ☐ ORIGINAL NEW CORRESPONDENCE |
| ☐ ADVERSE REACTION REPORT | ☐ PAPER NDA | ☐ FORMULATIVE REVIEW |
| ☐ MANUFACTURING CHANGE/ADDITION | ☐ CONTROL SUPPLEMENT | ☐ OTHER *(Specify below)* |
| ☐ MEETING PLANNED BY _____ | | |

**II. BIOMETRICS**

| STATISTICAL EVALUATION BRANCH | STATISTICAL APPLICATION BRANCH |
|---|---|
| ☐ TYPE A OR B NDA REVIEW | ☐ CHEMISTRY |
| ☐ END OF PHASE II MEETING | ☐ PHARMACOLOGY |
| ☐ CONTROLLED STUDIES | ☐ BIOPHARMACEUTICS |
| ☐ PROTOCOL REVIEW | ☐ OTHER |
| ☐ OTHER | |

**III. BIOPHARMACEUTICS**

| | |
|---|---|
| ☐ DISSOLUTION | ☐ DEFICIENCY LETTER RESPONSE |
| ☐ BIOAVAILABLITY STUDIES | ☐ PROTOCOL-BIOPHARMACEUTICS |
| ☐ PHASE IV STUDIES | ☐ *IN-VIVO* WAIVER REQUEST |

**IV. DRUG EXPERIENCE**

| | |
|---|---|
| ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | ☐ SUMMARY OF ADVERSE EXPERIENCE |
| ☐ CASE REPORTS OF SPECIFIC REACTIONS *(List below)* | ☐ POISON RISK ANALYSIS |
| ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

**V. SCIENTIFIC INVESTIGATIONS**

| | |
|---|---|
| ☐ CLINICAL | ☐ PRECLINICAL |

**COMMENTS/SPECIAL INSTRUCTIONS** *(Attach additional sheets if necessary)*:

**Please evaluate** [redacted] sterilization process, proposed sterility specifications and sterility validation data for the drug product, Levalbuterol hydrochloride Inhalation Solution. The drug product follows compendial method USP <71> for sterility testing and meets the USP requirements for sterility. The sterility validation report is provided in section 4.A.III.k (p 001 - 0206/Vol 1.05) of the submission.

The product composition (p265, Vol 1.03) is provided on the following page with this consult. The product is manufactured as unit dose vial using [redacted] The bulk drug product solution is [redacted] sterilized using [redacted] prior to filling of the vials. The [redacted] machine features a [redacted] sterilization cycle for minimum of [redacted] min. It should be noted that there is no microbial limit test for the drug substance, levalbuterol hydrochloride.

| | |
|---|---|
| CC:<br>☒ Orig. NDA ☒ HFD-570 Div. File ☒ CSO/Plant | ☒ Chemist/ VShah ☒ Chemistry TL/GPoochikian |
| SIGNATURE OF REQUESTER /S/ 02-10-1998 | METHOD OF DELIVERY *(Check one)*<br>☐ MAIL ☑ HAND |
| SIGNATURE OF RECEIVER | SIGNATURE OF DELIVERER |

**Drug Product Composition:**

1. Quantitative Composition:

| Component | 1.25 mg* Levalbuterol (mg/3 mL of product) | 0.63 mg* Levalbuterol (mg/3 mL of product) | |
|---|---|---|---|
| Levalbuterol HCl | 1.44 mg | | |
| Sodium Chloride | | | |
| Sulfuric Acid | | | |
| | | | |

* As levalbuterol base (molecular weight ratio = 239.3/275.8 = 0.868)

2. Batch Formula: Levalbuterol HCl Inhalation Solution
(Three Unit Dose Formulations)

| Component<br>Batch Size | 1.25 mg* Levalbuterol (mg/3 mL of product) | 0.63 mg* Levalbuterol (mg/3 mL of product) | |
|---|---|---|---|
| Levalbuterol HCl | | | |
| Sodium Chloride | | | |
| Sulfuric Acid, | | | |
| | | | |
| | | | |

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APR 28 1998

**REVIEW FOR HFD-570**

**OFFICE OF NEW DRUG CHEMISTRY**
**MICROBIOLOGY STAFF HFD-805**
**Microbiologist's Review #1 of NDA 20-837**
**April 27, 1998**

A. 1. **APPLICATION NUMBER:** 20-837

**APPLICANT:** Sepracor Inc.
111 Locke Drive
Marlborough, MA 01752
(508) 481-7683

2. **PRODUCT NAME:** [redacted] Inhalation Solution

3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:** Sterile levalbuterol HCl inhalation solution ([redacted] 0.63 mg, and 1.25 mg) packaged in unit dose [redacted] 3 mL LDPE bottles. Administration via nebulization.

4. **METHODS OF STERILIZATION:** [redacted]

5. **PHARMALOGICAL CATAGORY and/or PRINCIPLE INDICATION:** Beta$_2$-adrenergic receptor antagonist indicated for the treatment or prevention of [redacted] bronchospasm.

6. **DRUG PRIORITY CLASSIFICATION:** 3S

B. 1. **DATE OF INITIAL SUBMISSION:** June ~~July~~ 30, 1997

2. **RELATED DOCUMENTS:** (none)

3. **DATE OF CONSULT:** February 10, 1998

4. **ASSIGNED FOR REVIEW:** February 18, 1998

C. **REMARKS:** In contrast with the racemic albuterol sulfate (containing equal amounts of (R)- and (S)-enantiomers, levalbuterol consists solely of the active (R)-enantiomer.

APPEARS THIS WAY
ON ORIGINAL

## D. CONCLUSIONS:

The submission is not recommended for approval for microbiology issues concerning sterility assurance.

/S/ 4/28/98
Neal Sweeney, Ph.D.
/S/ 4/28/98

cc: NDA 20-837
HFD-570/Division File
HFD-570/CSO/P. Jani
HFD-570/Chemist/V. Shah
HFD-805/Consult File/N. Sweeney

Drafted by: N. Sweeney, April 27, 1998
R/D initialed by P. Cooney, April 27, 1998

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