CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-837

MICROBIOLOGY REVIEW(S)
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. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION: Beta-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


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
A. 1. APPLICATION NUMBER: 20-837

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

2. PRODUCT NAME: 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 bottles. Administration via nebulization.

4. METHODS OF STERILIZATION: 

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION: Beta-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. 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/
4/16/98

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
ON ORIGINAL
Redacted 3 pages of trade secret and/or confidential commercial information
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Supervisory Microbiologist HFD-160

FROM: Vibhakar J. Shah (HFD-820)

DATE: February 10, 1998
IND NO.: 20837
NAME OF DRUG: Levalbuterol-HCl Inhalation Solution
NAME OF FIRM: Sepracor Inc. 111, Locke Drive, Marlborough, MA 01752;
Tel: (508) 481-6700
Fax: (508) 481-7683

REQUEST FOR CONSULTATION

DATE: July 30, 1997
IND NO.: 20837
CLASSIFICATION OF DRUG: S
DESIRED COMPLETION DATE: 7/11/98

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

- TYPE A OR B NDA REVIEW
- END OF PHASE II MEETING
- CONTROLLED STUDIES
- PROTOCOL REVIEW
- OTHER

III. BIOPHARMACEUTICS

- ASSUSSION
- BIOAVAILABILITY STUDIES
- PHASE IV STUDIES
- OTHER

- CHEMISTRY
- PHARMACOLOGY
- BIOPHARMACEUTICS
- OTHER

IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMILOGY PROTOCOL
- DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- CASE REPORTS OF SPECIFIC REACTIONS (List below)
- COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- DEFICIENCY LETTER RESPONSE
- PROTOCOL-BIOPHARMACEUTICS
- IN-VIVO WAIVER REQUEST
- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- SUMMARY OF ADVERSE EXPERIENCE
- POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- CLINICAL
- PRECLINICAL

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

Please evaluate 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.II.3.k (p 001 - 0206/3ol.05) of the submission.

The product composition (c265, Vol 1.03) is provided on the following page with this consult. The product is manufactured as unit dose vial using the bulk drug product solution is sterilized using prior to filling of the vials. The machine features a sterilization cycle for a minimum of min. It should be noted that there is no microbial limit test for the drug substance, Levalbuterol hydrochloride.

CC: Orig. NDA HFD-570 Div. File CSO/Pjani Chemist/ VShah Chemistry TL/GPochikian

SIGNATURE OF REQUESTER: /s/ 02-10-1998

METHOD OF DELIVERY (Check one) MAIL HAND

SIGNATURE OF DELIVERER: /s/
Drug Product Composition:

1. Quantitative Composition:

<table>
<thead>
<tr>
<th>Component</th>
<th>1.25 mg* Levalbuterol (mg/3 mL of product)</th>
<th>0.63 mg* Levalbuterol (mg/3 mL of product)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levalbuterol HCl</td>
<td>1.44 mg</td>
<td></td>
</tr>
<tr>
<td>Sodium Chloride</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfuric Acid</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

2. Batch Formula: Levalbuterol HCl Inhalation Solution (Three Unit Dose Formulations)
A. 1. APPLICATION NUMBER: 20-837

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

2. PRODUCT NAME: 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 bottles. Administration via nebulization.

4. METHODS OF STERILIZATION: 

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION: Beta-adrenergic receptor antagonist indicated for the treatment or prevention of bronchospasm.

6. DRUG PRIORITY CLASSIFICATION: 3S

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

2. RELATED DOCUMENTS: (none)


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.

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

APPEARS THIS WAY ON ORIGINAL