CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-912

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

NDA NUMBER
21-912

NAME OF APPLICANT / NDA HOLDER
SEPRACOR INC.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
TO BE DETERMINED

ACTIVE INGREDIENT(S)	STRENGTH(S)
arformoterol tartrate	**22 mcg arformoterol tartrate (equivalent to 15 mcg of arformoterol free base) in a 2 ml unit-dose vial**

DOSAGE FORM
unit-dose vial

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,795,564	**August 18, 1998**	**April 3, 2012**

d. Name of Patent Owner
SEPRACOR INC.

Address *(of Patent Owner)*
84 Waterford Drive

City/State
Marlborough, MA

ZIP Code	FAX Number *(if available)*
01752	**(508) 357-7894**
Telephone Number	E-Mail Address *(if available)*
(508) 357-7386	

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address *(of agent or representative named in 1.e.)*

City/State

ZIP Code	FAX Number *(if available)*
Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No

4.2 Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?		
1		☒ Yes	☐ No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*

Indication and Usage: Long term maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema

Labeling References:

(Continued on attached Page 2-A)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Kristina L Burgard	28 November 2005

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Kristina L. Burgard, Chief Intellectual Property Counsel, Sepracor Inc.	
Address 84 Waterford Drive	City/State Marlborough, MA
ZIP Code 01752	Telephone Number (508) 357-7386
FAX Number *(if available)* (508) 357-7894	E-Mail Address *(if available)* kristina.burgard@sepracor.com

EXCLUSIVITY SUMMARY

NDA # 21-912 SUPPL # HFD # 570

Trade Name Brovan

Generic Name arformoterol inhalation solution

Applicant Name Sepracor

Approval Date, If Known October 6, 2006

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 questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

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

505 (b)(1)

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

YES ☒ 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 ☒ NO ☐

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

5

e) Has pediatric exclusivity been granted for this Active Moiety?
YES ☐ NO ☒

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

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

2. Is this drug product or indication a DESI upgrade?
YES ☐ NO ☒

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES ☒ NO ☐

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

NDA# 20-831 Foradil Aerolizer (formoterol fumarate

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 NDAs 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 ☒ 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 ☒ 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 ☒

(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 ☒

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:

091-050 Safety and Efficacy

091-051 Safety and Efficacy

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 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

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 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a

similar investigation was relied on:

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

091-050 Safety and Efficacy and 091-051 Safety and Efficacy

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

IND ☐ ☐ YES ☒ ! NO ☐ b(4)
! Explain:

Investigation #2

IND ☐ ☐ YES ☒ ! NO ☐ b(4)
! 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 ☒

If yes, explain:

Name of person completing form: Ladan Jafari
Title: Regulatory Health Project Manager
Date: October 4, 2006

Name of Office/Division Director signing form: Badrul Chowdhury, M.D., Ph.D.
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Badrul Chowdhury
10/10/2006 04:14:10 PM

3/1/06

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # 21-912_____ Supplement Type (e.g. SE5):_____ Supplement Number:

Stamp Date: 12/12/05 Action Date: N/A

HFD 570 Trade and generic names/dosage form: arformoterol tartrate inhalation solution

Applicant: Sepracor Therapeutic Class: Respiratory

Indication(s) previously approved: N/A

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

Number of indications for this application(s): 1

Indication #1: COPD

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

XYes: 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
XDisease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Other:_____

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	kg_____	mo._____	yr._____	Tanner Stage_____
Max_____	kg_____	mo._____	yr._____	Tanner Stage_____

Reason(s) for partial waiver:

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

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

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

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

Other:_____

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

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

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

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

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA 21-912
HFD-960/ Grace Carmouze

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

(revised 12-22-03)

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

/s/

Ladan Jafari
3/1/2006 04:11:19 PM

1 Request for a Full Waiver of Pediatric Studies

In accordance with the provisions contained in 21 CFR 201.23(c)(1), Sepracor does not plan to conduct studies in the pediatric population for a COPD indication with the new drug Arformoterol Tartrate Inhalation Solution. As previously agreed in communications with the Division of Pulmonary and Allergy Drug Products (DPADP), and pursuant to the provisions of 21 CFR 314.55(c)(2), Sepracor is hereby requesting a Full Waiver of the requirement to conduct Pediatric Studies based on the following:

- The indication proposed for Arformoterol Tartrate Inhalation Solution, the treatment of COPD, a disease not present in the pediatric population.
- At the IND End-of-Phase 2 (EOP2) Meeting on 06 September 2001, Sepracor stated the intention to request full waiver of the requirement to conduct research in any pediatric population. The Division acknowledged that a pediatric waiver would likely be granted for a COPD indication.

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 Arformoterol Tartrate Inhalation Solution.

Renee M Carroll 08Nov05

Renee M. Carroll, MS, RAC Date
Associate Director, Regulatory Affairs

SEPRACOR

04 October 2006

Badrul Chowdhury, M.D.
Director, Division of Pulmonary and Allergy Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: **NDA 21-912: Arformoterol Tartrate Inhalation Solution**
General Correspondence: Proposed Post Marketing Commitments

Dear Dr. Chowdhury:

Please reference Sepracor Inc.'s NDA 21-912 for Arformoterol Tartrate Inhalation Solution submitted on 08 December 2005. Please also reference a facsimile correspondence dated 02 October 2006 wherein the Division outlined proposed post marketing study commitments.

Sepracor agrees to the post marketing study commitments, numbered 1-3 (see Attachment 1), as outlined in the facsimile dated 02 October 2006. Our proposals for the protocol submission dates, study start dates, and final report submission dates for these commitments are provided in Attachment 1.

We recognize that the details of the study designs will require further interactions with the Division. As such, the proposed protocol submission and study start dates reflect our current estimate of the study preparation time required for each study commitment. We have also factored into these dates some time for the Division to review, provide feedback, and approve the protocols we will propose. The dates we have listed for protocol submissions are the dates by which we anticipate that Division reviews and approvals will be completed, and therefore are the dates of final protocol submissions.

Sepracor also agrees to submit the final study reports to the NDA as a supplement.

Appears This Way
On Original

The following is background information to support your review of our proposed approaches and dates.

[redacted] b(4)

We look forward to working with the Division in developing the protocols for these post marketing study commitments.

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 Electronic Submissions in Electronic Format – NDAs;* IT 3, January 1999. The archival copy of the amendment comprises the following:

1. One (1) CD-ROM containing the amendment in electronic format. The amendment is approximately 1 MB in size and is located in folder *N21912*. The files on the CD-ROM have been scanned for viruses with Network Associates VirusScan Enterprise version 8.0.0 with a Virus definition of 4866, dated 04 October 2006. The electronic archival copy will serve as the electronic review copy.

2. One paper volume containing the original signed Cover Letter and Form FDA 356h.

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

	Location
Cover Letter	*N21912\cover.pdf*
Form FDA 356h	*N21912\356h.pdf*
Table of Contents (Amendment Index)	*N21912\amendtoc.pdf*

If you have any questions or need additional information, please contact me by telephone at (508) 357-7598 or by fax at (508) 357-7491.

Sincerely,

Reneé M. Carroll
Associate Director, Regulatory Affairs

Enclosures

Attachment 1
Proposed Post Marketing Study Commitments

1. To conduct a multicenter, randomized, placebo-controlled, large, simple safety trial to evaluate the effects of long term use of BROVANA (arformoterol tartrate) Inhalation Solution in patients with COPD. The objective of this trial is to determine the risk of fatal and life-threatening respiratory events associated with the long term use of BROVANA in patients with COPD. The trial will be of adequate size and duration to meet the objective.

   Protocol Submission Date: August 2007
   Study Start Date: December 2007
   Final Report Submission Date: December 2012

2. To conduct a safety and tolerability study with one or more doses and one or more dose levels of BROVANA (arformoterol tartrate) Inhalation Solution in children with asthma and/or obstructive airway disease. The objective of this study is to assess the safety and tolerability of BROVANA in children 12 years of age and younger with asthma. The study will include a placebo or active control treatment group, as appropriate. The study will also include children age 12 years and younger so that the lower age limit is based upon the age at which asthma/obstructive airway disease exists. The trial will be of adequate size and duration to meet the objective.

   Protocol Submission Date: June 2007
   Study Start Date: September 2007
   Final Report Submission Date: December 2008

3. To conduct a safety and efficacy study with one or more doses and one or more dose levels of BROVANA (arformoterol tartrate) Inhalation Solution in children with asthma and/or obstructive airway disease presenting with an acute exacerbation. The objective of this study is to establish the safety and efficacy of BROVANA in children 12 years of age and younger with an acute exacerbation of asthma. The study will include a placebo or active control treatment group, as appropriate. The study will also include children age 12 years and younger so that the lower age limit is based upon the age at which asthma/obstructive airway disease exists. The trial will be of adequate size and duration to meet the objective.

   Protocol Submission Date: September 2008
   Study Start Date: January 2009
   Final Report Submission Date: May 2011

NDA 21-912
Page 1

Dear Ms. Carroll:

Attached please find the responses to your recent proposal regarding the labeling submitted on October 2, 2006. Also, please note that DMETS did not find the tradename [redacted] acceptable. Please use the alternative tradename "Brovana" in all of your proposed labeling, container, carton, and medication guide.

b(4)

Let me know if you have any questions.

Ladan Jafari, Regulatory Health Project Manager

14 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 1

Drafted by: LJ/10-3-06

Initialed by: Seymour
Durmowicz
Chowdhury

Filename: N 21912revised.doc

NDA 21-912

Dear Ms. Carroll:

Attached please find the revised labeling and medication guide for your arformtoterol application. We ask that you submit your revised labeling incorporating these changes by COB on Tuesday October 3, 2006.

We also have the following comment:

[redacted] b(4)

I may be reached at 301-796-1231 for any questions.

Ladan Jafari, Regulatory Health 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/

Ladan Jafari
10/3/2006 11:16:25 AM
CSO

31 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 2

4 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 3

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-912

DISCIPLINE REVIEW LETTER

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

Attention: Renee M. Carroll, M.S., RAC
Associate Director, Regulatory Affairs

Dear Ms. Carroll:

Please refer to your December 8, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for arformoterol tartrate inhalation solution.

We also refer to your submission dated March 31 and April 18, 2006.

Our review of the Chemistry, Manufacturing and Controls section of your submission is complete, and we have identified the following deficiencies:

1. The following comments pertain to the drug substance:

b(4)

b(4)

b(4)

b(4)

2 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 4

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/s/

Blair Fraser
6/27/2006 03:00:52 PM

MEMORANDUM

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

DATE: September 14, 2006

TO: Badrul Chowdhury, M.D., Director
Division of Pulmonary and Allergy Products

VIA: Ladan Jafari, Regulatory Project Manager
Division of Pulmonary and Allergy Products

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support

THROUGH: Solomon Iyasu, M.D., M.P.H., Director
Division of Surveillance, Research, and Communication Support

SUBJECT: DSRCS Medication Guide review for Tradename (arfomoterol tartrate) Inhalation Solution, NDA 21-912.

Background and Summary

The sponsor submitted an NDA for Tradename (arfomoterol tartrate) Inhalation Solution, NDA 21-912, on January 3, 2006. Arfomoterol tartrate is a long-acting beta$_2$-agonist medicine (LABA), submitted "for twice daily (morning and evening) long term maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema."

The sponsor submitted draft *Patient Instructions for Use* with the NDA Submission. A Medication Guide is required for all LABA products that contain an asthma indication, to address the serious and significant public health concern of an increase risk of asthma-related death found in patients receiving a LABA medication in a large placebo-controlled US study. A regulatory Briefing was held on August 25, 2006, and it was decided that this product would contain a Boxed WARNING regarding the increase risk of asthma-related death with LABAs in patients with asthma and a Medication Guide to adequately warn prescribers and patients because of the concern of off-label use with this product.

We have drafted a Medication Guide using the approved Foradil Medication as a template and incorporating product-specific information. We have also revised and appended the *Instructions for Use* at the end of the MG. Our revisions to the *Instructions for Use* were done to simplify wording to increase patient comprehension.

Comments to the review division are bolded, italicized, and underlined. Please call us if you have any questions.

6 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 5

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/s/

Jeanine Best
9/14/2006 10:41:53 AM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
9/14/2006 10:44:04 AM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

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

DATE: June 1, 2006

TO: Badrul Chowdhury, M.D., Director
Division of Pulmonary and Allergy Products

VIA: Ladan Jafari, Regulatory Project Manager
Division of Pulmonary and Allergy Products

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support

THROUGH: Toni Piazza-Hepp, Pharm.D., Deputy Director
Division of Surveillance, Research, and Communication Support

SUBJECT: DSRCS Patient Labeling Review for Tradename (arfomoterol tartrate) Inhalation Solution, NDA 21-912

Background and Summary

The sponsor submitted an NDA for Tradename (arfomoterol tartrate) Inhalation Solution, NDA 21-912, on January 3, 2006. Arfomoterol tartrate is a long-acting beta$_2$-agonist medicine (LABA), submitted "for twice daily (morning and evening) long term maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema."

The sponsor submitted draft *Patient Instructions for Use* with the NDA Submission. A Medication Guide is required for all LABA products that contain an asthma indication, to address the serious and significant public health concern of an increase risk of asthma-related death found in patients receiving a LABA medication in a large placebo-controlled US study. At this time it has been decided that a Medication Guide will not be required for a LABA product that lacks an asthma indication.

See the attached for our suggested revisions to the *draft Patient Instructions for Use*. We have expanded the *draft Patient Instructions for Use* to include more comprehensive patient information. We have used the patient-friendly format that we are recommending for all patient information, although, this format is not required for voluntary Patient Information. We have simplified and revised the *draft Patient Instructions for Use* and placed them at the end of the Patient Information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

8 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Jeanine Best
6/1/2006 03:23:52 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
6/1/2006 04:01:26 PM
DRUG SAFETY OFFICE REVIEWER

NDA 21-912

Dear Ms. Carroll:

We are reviewing your NDA for arformoterol tartrate inhalation solution and we have the following requests for information. We ask that you provide this information to us by April 3, 2006, so that we can continue our review of your application.

Reference is made to the study report titled A 24-MONTH INHALATION ONCOGENICITY STUDY OF (R,R)-FORMOTEROL IN RATS — 312051), as well as rat data files 312051FT.xpt and 312051MT.xpt submitted as SAS transport files. We have found discrepancies in the type of death (i.e., found dead, terminal sacrifice, etc.) between that reported in the study report and in the data files. For example, animal number 7595 was marked as "FOUND DEAD" in Table 38 (Individual Survival and Disposition) on page 823 of Tables section. The same animal was reported in the data set as terminal sacrificed (DTHSACST=2, according to DEFIND.PDF). Such discrepancies can be found across dose groups in male- and female-rat data sets. b(4)

1. Identify all animals with such discrepancies, described above, and fully explain why such discrepancies occurred.

2. Reconcile either the study report or data files animal by animal as to the final disposition of the animal (i.e., found dead, euthanized in extremis, or scheduled euthanasia) and the study day of its final disposition.

I may be reached at 301-796-1231 for any questions.

Ladan Jafari, Regulatory Health Project Manager

NDA 21-912

Drafted by: LJ/3-21-06

Initialed by: Barnes/3-22-06
Robison/3-23-06
McGovern for Sun/3-23-06
Guo/3-23-06
Davi/3-23-06

Filename: N21912preclincomments.doc

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/s/

Ladan Jafari
3/23/2006 11:47:46 AM
CSO

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-912 Supplement # Efficacy Supplement Type SE-

Trade Name: Arformoterol tartrate Inhalation Solution
Established Name: arformoterol tartrate
Strengths: 15 mcg/2 mL

Applicant: Sepracor, Inc.
Agent for Applicant: N/A

Date of Application: December 8, 2005
Date of Receipt: December 12, 2005
Date clock started after UN: N/A
Date of Filing Meeting: February 3, 2006
Filing Date: February 10, 2006
Action Goal Date (optional): August 12, 2006 User Fee Goal Date: October 12, 2006

Indication(s) requested: COPD

Type of Original NDA: (b)(1) X (b)(2) ☐
OR
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

X NDA is a (b)(1) application OR ☐ NDA is a (b)(2) application

Therapeutic Classification: S X P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.) N/A

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

User Fee Status: Paid X Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling.*

If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES ☐ NO X
  If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO X

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO X
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

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

- Was form 356h included with an authorized signature? YES X NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES X NO ☐
  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A ☐ YES X NO ☐
  If an electronic NDA, all forms and certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format? All electronic submission.

  Additional comments: N/A

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A X YES ☐ NO ☐

- Is it an electronic CTD (eCTD)? N/A ☐ YES ☐ NO X
  If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

  Additional comments: N/A

- Patent information submitted on form FDA 3542a? YES X NO ☐

- Exclusivity requested? YES, 5 Years NO ☐
  ***NOTE:** An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES X NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."

- Financial Disclosure forms included with authorized signature? YES X NO ☐
  (Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y X NO ☐

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

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 55,302

- End-of-Phase 2 Meeting(s)? Date(s) 9/6/01 (CMC), 9/6-01 (all other disciplines) NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) 3/7/05 NO ☐
  If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES X NO ☐
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES X NO ☐

- Risk Management Plan consulted to ODS/IO? N/A ☐ YES X NO ☐

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y X NO ☐

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ☐ YES X NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A X YES ☐ NO ☐

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A X YES ☐ NO ☐

- Has DOTCDP been notified of the OTC switch application? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES X NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES ☐ NO ☐
- Establishment Evaluation Request (EER) submitted to DMPQ? YES X NO ☐
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: 2/3/06

BACKGROUND: Arformoterol is a long acting beta agonist, which is an enantiomer of formoterol. Racemic formoterol is currently approved and is marketed as a dry powder for inhalation. Arformoterol is formulated as a solution for nebulization and is being evaluated for COPD indication.

ATTENDEES: Gene Sullivan, Badrul Chowdhury, Shinja kim, Emmanuel Fadiran, Ted Guo, Ruthie Davi, Art Shaw, Chien Hua Niu, Tim Robison, Joe Sun, Miranda Raggio, Ladan Jafari

ASSIGNED REVIEWERS (including those not present at filing meeting) : Tony Durmowicz, Shinja kim, Ted Guo, Chien Hua Niu, Tim Robison

Discipline	**Reviewer**
Medical:	Tony Durmowicz
Secondary Medical:	Gene Sullivan
Statistical:	Ted Guo
Pharmacology:	Tim Robison
Statistical Pharmacology:	Karl Lin
Chemistry:	Chien Hua Niu
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	Shinja Kim
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	N/A
Regulatory Project Management:	Ladan Jafari
Other Consults:	ODS/DDMAC

Per reviewers, are all parts in English or English translation? YES X NO ☐
If no, explain:

CLINICAL FILE X REFUSE TO FILE ☐

- Clinical site inspection needed? YES ☐ NO X
- Advisory Committee Meeting needed? YES, date if known _____ NO X
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A X YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A X FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE X REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE X REFUSE TO FILE ☐

- Biopharm. inspection needed? YES ☐ NO X

PHARMACOLOGY N/A ☐ FILE X REFUSE TO FILE ☐

- GLP inspection needed? YES ☐ NO X

CHEMISTRY FILE X REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☐ NO ☐
- Microbiology YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments: N/A

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

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

☐ No filing issues have been identified.

X Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1.☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

2.☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

3.X Convey document filing issues/no filing issues to applicant by Day 74.

Ladan Jafari
Regulatory Project Manager, HFD-

Appendix A to NDA Regulatory Filing Review

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).

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☐

   If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES ☐ NO ☐

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

   If "No," skip to question 4. Otherwise, answer part (b).

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

   If "Yes," skip to question 6. Otherwise, answer part (c).

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES ☐ NO ☐

   If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☐

   (***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

   If "No," skip to question 5. Otherwise, answer part (b).

   (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

   NOTE: *If there is more than one pharmaceutical alternative approved, consult the Director, Division of*

Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

If "Yes," skip to question 6. Otherwise, answer part (c).

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES ☐ NO ☐

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES ☐ NO ☐

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

(b) Is the approved drug product cited as the listed drug? YES ☐ NO ☐

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☐

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☐

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO ☐

10. Are there certifications for each of the patents listed for the listed drug(s)? YES ☐ NO ☐

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

  YES ☐ NO ☐

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  N/A ☐ YES ☐ NO ☐

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

  N/A ☐ YES ☐ NO ☐

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

  YES ☐ NO ☐

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

  YES ☐ NO ☐

- EITHER

  The number of the applicant's IND under which the studies essential to approval were conducted.

  IND# _____ NO ☐

  OR

  A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

  YES ☐ NO ☐

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES ☐ NO ☐

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/s/

Ladan Jafari
3/1/2006 04:30:36 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-912

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

Attention: Reneé M. Carroll, M.S., RAC
Associate Director, Regulatory Affairs

Dear Ms. Carol:

Please refer to your December 8, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for arformoterol tartrate inhalation solution.

We also refer to your submissions dated December 20, 2005, and January 3, and 6, 2006.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on February 10, 2006, in accordance with 21 CFR 314.101(a).

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

1. As discussed during the telephone conference on August 15, 2005, the limited available data in racial and ethnic subgroups will be considered during the NDA review. We encourage you to generate safety and efficacy data in these populations.

2. On November 18, 2005, the FDA issued a public health advisory regarding risks associated with long-acting beta2-agonists in patients with asthma (http://www.fda.gov/cder/drug/advisory/LABA.htm). This advisory states that manufacturers of marketed long-acting beta2-agonists indicated for the treatment of asthma were asked to update their existing product labels with new warnings and a Medication Guide. The advisory also states that information is not available to know whether there are similar concerns in patients with COPD. During the course of the review of your NDA we will consider how this issue should be addressed in the product label, and whether further data to explore this issue, such as a large, simple, safety study, will be requested.

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

If you have any questions, call Ms. Ladan Jafari, Regulatory Project Manager, at (301) 796-1231.

Sincerely,

{See appended electronic signature page}

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

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/s/

Badrul Chowdhury
2/23/2006 02:19:45 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-912

NDA ACKNOWLEDGMENT

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

Attention: Renee M. Carroll, M.S., RAC
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: Arformoterol tartrate Inhalation [ ] b(4)

Review Priority Classification: Standard (S)

Date of Application: December 8, 2005

Date of Receipt: December 12, 2005

Our Reference Number: 21-912

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 10, 2006, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 12, 2006.

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

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary & Allergy Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call Ms. Ladan Jafari, Regulatory Project Manager, at (301) 796-1231.

Sincerely,

{See appended electronic signature page}

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

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/s/

Badrul Chowdhury
1/25/2006 05:18:18 PM

SEPRACOR

08 December 2005

Badrul Chowdhury, M.D.
Director, Division of Pulmonary and Allergy Drug Products, HFD-570
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: **NDA 21-912**
Arformoterol Tartrate Inhalation Solution
Original New Drug Application

Dear Dr. Chowdhury:

Pursuant to Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act, Sepracor Inc. is hereby submitting an original New Drug Application for Arformoterol Tartrate Inhalation Solution for the long term maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

Arformoterol, a long acting beta agonist, is the (R,R)-enantiomer of formoterol. Racemic formoterol is currently approved and is marketed as a dry powder for inhalation. Arformoterol is formulated as a solution for nebulization, a delivery option that may be important for patients with COPD.

This NDA application contains data from 16 completed clinical studies (conducted under IND 55,302), including two Phase 2 dose ranging studies (091-021 and 091-026), two 12 week pivotal studies (091-050 and 091-051), and one 12 month safety study (091-060). These studies provide justification for the dose proposed for marketing (15 μg BID) and demonstrate that this dose is safe and effective for the proposed indication.

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*). The NDA is a hybrid application because the

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

Appears This Way
On Original

Chemistry, Manufacturing, and Controls (CMC) section and CMC summary section of NDA Section 3 are prepared in Common Technical Document (CTD) format, in accordance with pre-NDA guidance provided by the Division. All other sections are presented in traditional NDA format.

In accordance with the recently implemented Guidance for Industry entitled "Providing Regulatory Submissions in Electronic Format – Content of Labeling (April 2005), Sepracor is also providing the proposed package insert labeling using extensible markup language (XML) based on the Health Level 7 (HL7) Structured Product Labeling (SPL) specifications.

This electronic submission is being provided on one DLT (40/80) tape formatted using NT server 4.0 with NT backup. The size of this electronic submission is approximately 30 gigabytes. Sepracor certifies that the data on this tape have been scanned for viruses with Network Associates VirusScan Enterprise 7.0.0 with a Virus Definition of 4644 dated 06 December 2005. The electronic archival copy will serve as the electronic review copy.

As agreed with the Division, we are providing six desk copies of the archival Volume 1. Archival Volume 1, is provided with this electronic NDA and 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 (NDA Section 5, Nonclinical Pharmacology and Toxicology)
- GCP Compliance Statement (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 New England District Office of the FDA that NDA 21-912 has been submitted.

The user fee number for this NDA 21-912 is PD3006283. Sepracor paid the user fee on 14 November 2005.

Information concerning patents is provided in Sections 13 and 14 of this submission. Information on four US patents (US Pat. Nos. 5,795,564; 6,068,833; 6,589,508; and 6,866,839) is provided, and these patents are applicable to the product described in this application.

As previously agreed in communications with the Division, and pursuant to the provisions of 21 CFR § 314.55(c)(2), Sepracor is requesting a Full Waiver of the requirement to conduct Pediatric Studies. This request is provided in NDA Section 20.1 (*reghistory.pdf*).

We appreciate the guidance that has been provided to us by the Division 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 me by telephone at (508) 357-7598 or by fax at (508) 357-7491.

Sincerely,

Reneé M. Carroll
Associate Director, Regulatory Affairs

November 8, 2005

Food and Drug Administration (360909)
Mellon Client Service Center RM 670
500 Ross Street
Pittsburgh, PA 15262-0001

Re: **NDA 21-912: TRADENAME (arformoterol tartrate) Inhalation Solution**
Use Fee I.D. Number PD 3006283
Payment of User Fee

Enclosed is our check number 37151 in the amount of $767,400.00 (User Fee I.D. Number PD 3006283) representing payment in full of the user fee for NDA 21-912 [TRADENAME (arformoterol tartrate) Inhalation Solution] as stipulated in the Federal Food, Drug and Cosmetic Act and as amended by the Prescription Drug User Fee Act of 2002 (PDUFA III).

If you have any questions or comments regarding this submission, please contact me by telephone at (508) 357-7598 or via fax at (508)-357-7491.

Sincerely,

Renee M. Carroll

Renee M. Carroll, M.S., RAC
Associate Director, Regulatory Affairs

Enclosures

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

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

/s/

Craig Ostroff
7/3/02 10:35:55 AM

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	PRESCRIPTION DRUG USER FEE COVERSHEET

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
Renee Carroll
84 Waterford Dr
Marlborough MA 01752-7010
US

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

N021912

2. TELEPHONE NUMBER
508-357-7598

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

[X] 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:

[X] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

[ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

N021912

3. PRODUCT NAME
Arformoterol Tartrate Inhalation Solution

6. USER FEE I.D. NUMBER
PD3006283

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

[ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food,Drug, and Cosmetic Act

[ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] NO

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewinginstructions, 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 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
Renee M Carroll	Ass Director, RA	08 Nov 05

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
$767,400.00

Form FDA 3397 (12/03)

IBE_PRMT_CLOSE_G) (Print Cover sheet)

Memorandum of Meeting Minutes Facsimile Correspondence

Date: March 28, 2005

To: Renee M. Carroll, M.S., RAC
Associate Director, Regulatory Affairs

Fax: 508-357-7491

From: Akilah Green
Regulatory Project Manager

Subject: IND 55,302/Arformoterol Inhalation Solution
March 7, 2005, meeting minutes

Reference is made to the meeting held between representatives of your company and this Division on March 7, 2005. 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.

MEMORANDUM OF MEETING MINUTES

MEETING DATE: March 7, 2005

TIME: 1:30 – 3:00 PM

LOCATION: Food and Drug Administration

APPLICATION: IND 55,302/Arformoterol Inhalation Solution/Sepracor
Type B/Pre-NDA Meeting

SEPRACOR REPRESENTATIVES:

Rudolf Baumgartner, M.D., Vice President, Clinical Research
Renee Carroll, M.S., RAC, Associate Director, Regulatory Affairs
Lisa Curry, Associate Director, Regulatory Affairs
Donna Grogan, M.D., Senior Vice President, Clinical Research
John Hanrahan, M.D., Senior Medical Director, Pulmonary-Immunology, Clinical Research
Cindy Kirk, Ph.D., Vice President, Regulatory Affairs
Gary Maier, Ph.D., Executive Director, Clinical Pharmacology
William McVicar, Ph.D., Executive Program Director
Stewart Mueller, Senior Vice President, Regulatory Affairs
David Reasner, Ph.D., Senior Vice President, Clinical Operations and Data Analysis
Kenneth Sciarappa, Ph.D., Principal Biostatistician

DIVISION OF PULMONARY AND DRUG PRODUCTS (DPAP) REPRESENTATIVES:

Badrul A. Chowdhury, M.D., Ph.D., Division Director
Peter Starke, M.D., Clinical Team Leader
John Gunkel, M.D., Clinical Reviewer
Warner Carr, M.D., Clinical Reviewer
Shinja R. Kim, Ph.D., Clinical Pharmacology and Biopharmaceutics Reviewer
Emmanuel Fadiran, Ph.D., Clinical Pharmacology and Biopharmaceutics Team Leader
Timothy Robison, Ph.D., Pharmacology/Toxicology Reviewer
C. Joe Sun, Ph.D., Pharmacology/Toxicology Team Leader
Sue Jane Wang, Ph.D., Acting BioStatistics Team Leader
Ted Guo, Ph.D., Biostatistics Reviewer
Akilah Green, BSN, MS, Regulatory Project Manager

BACKGROUND: Sepracor submitted a Pre-NDA meeting request dated December 9, 2004, to discuss their overall clinical and non-clinical development program. The meeting package was dated January 28, 2005. The Division responded to the questions in the meeting package by fax on March 4, 2005 (see below).

DISCUSSION: Each question from Sepracor is shown below, followed by the Division's response. After receiving the Division's faxed responses, Sepracor requested clarification at the meeting on the responses to questions 1, 2, 4, 5, and 9. The discussions are captured in italics below following the Division's response.

Question 1.

On the basis of the data described in the Clinical Dose Justification section of this package, Sepracor proposes that the 15 µg BID dose is the safe and effective ⊏ ⊐ ***dose for COPD patients. Does the Agency agree that the data support this proposed dose and are adequate to support the review and potential approval (pending review) of 15 µg BID as the*** ⊏ ⊐ b(4)

Response:

The Division cannot determine whether a dose is "safe and effective" until it has reviewed the NDA. The summary data provided in the briefing package support using the 15 µg dose in the pivotal clinical studies, but determining whether it is the optimal dose will be a review issue.

The Division added that Sepracor seemed to be seeking an agreement from the Division that the ⊏ ⊐ *proposed dose of 15 ug BID is a settled issue based on the pre-NDA summary package. The Division clarified that it is not. The data suggest that the 15 ug BID dose results in effective bronchodilatation, but the two Phase 2 dosing studies have not been reviewed and the final determination will be a review issue.* b(4)

Question 2.

Does the Agency agree that the data, as described in the meeting package, are adequate to support the review and potential approval (pending review) of the ⊏ ⊐ b(4)

Response:

⌜ b(4)

b(4)

⌟ b(4)

1 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 7

b(4)

Question 3.

Please confirm that the safety data comprising the 091-050 and 091-051 pivotal studies (12 weeks of treatment at doses of 15 mcg BID, 25 mcg BID, and 50 mcg QD) and the 091-060 long-term safety study (52 weeks of treatment at a dose of 50 mcg QD) are adequate in scope, and that the preliminary safety data presented in this meeting package support the applicability of the 52-week data to the review and potential approval (pending review) of all proposed doses.

Reponse:

- The overall safety database is minimal but acceptable.
- Adequate data for the highest dose would support lower doses as well.
- As noted at our meeting of February 9, 2004, whether the program adequately evaluated QT effects will be a review issue.
- The safety database should be complete at the time of NDA submission.

Question 4.

Is the overall arformoterol clinical program, including clinical pharmacology, adequate to support the review and potential approval (pending review) of chronic use of arformoterol for the long-term maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema?

Response:

Your clinical studies appear to have complied with the Division's recommendations regarding a primary efficacy endpoint in patients with COPD. Whether the studies were otherwise "adequate" will depend on the proposed labeling and the specific claims you intend to make.

The Division stated that the clinical program appears to be adequate, however, we are reserving judgment about whether the evaluation of QT prolongation will be adequate. At our February 9, 2004, meeting we indicated that a separate QT study might not be necessary if sufficient evaluation is present in the pivotal studies; however, we will need to see that data to make a final determination. The Division also referred Sepracor to the draft ICH E-14 guidance entitled "The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs.

Question 5.

Does the Agency agree with Sepracor's proposal for the presentation of the efficacy and safety data on arformoterol, including the rationale for the pooled analyses summarized above, and as described in the ISE and ISS outlines included in this package?

Response:

- We encourage you to adhere to Common Technical Document (CTD) format as described in the ICH M4 guidances.

- Your plans for pooling data are reasonable. Presentation of safety data in the package insert should be supported by the analyses presented in the ISS.

- ⊏ ⊐ b(4)

- Include race and ethnicity in your efficacy subgroup analyses, in addition to the other factors listed in your submission.

Sepracor stated that they did not include race and ethnicity in the planned efficacy analyses because there are such sparse data in the non-Caucasian group. The patient breakdown was about 95% Caucasian, 3-3.5% African American, 1-1.5% Asian, Hispanic, and other. The Division stated that Sepracor should present the race and ethnicity subgroup efficacy data nonetheless. The Division also indicated that the product labeling ⊏ ⊐ b(4)

Post-meeting Note:
The Division gave further consideration to this issue following the meeting, and determined that this is likely to be an important review issue. The lack of racial and ethnic subgroup data in the pivotal studies, resulting in under-represented subgroups, could be problematic to Sepracor's NDA application.

- Provide the actual p-value results, not just "$p<0.05$," for example.

Question 6.
Sepracor intends to create patient profiles for any patient who experienced a serious adverse event or an adverse event leading to discontinuation, including death. All the safety data collected for these subjects will be included in the patient profile. The patient profiles will be submitted as an appendix to the ISS? Does the Division concur with this approach?

Response:
The approach is acceptable. Case report forms for patients who died or discontinued because of serious adverse events must also be provided.

Question 7.
Sepracor plans to submit the archival copy of the NDA electronically. The FDA guidance entitled "Providing Regulatory Submissions in Electronic Format-NDAs" requires that a paper review copy of technical sections be submitted. Sepracor would like to propose waiving the paper review copy for all technical sections, referenced in the FDA guidance. Signature pages pertaining to the application will be provided in paper form. Does the Division concur with this proposal?

Response:
No. Adhere to the Guidance.

Question 8.
All pharmacology studies performed with arformoterol are outlined in Tables A and B of Appendix B. Does the Agency agree that the nonclinical pharmacology program is complete and adequate to support the review and potential approval (pending review) of arformoterol NDA?

Response:
Yes. Pending review, the nonclinical pharmacology program appears complete and adequate to support the review and potential approval of the NDA.

Question 9.
Two carcinogenicity study reports (090-828, 090-833) were submitted to the Agency on 03 November 2004 (Serial No. 349) and 21 October 2004 (Serial No. 347), respectively, and are summarized in Section 5.2.2.4. Does the Agency agree that these studies, as submitted, are sufficient to determine the carcinogenic risk of arformoterol?

Response:
The mouse and rat carcinogenicity studies are under active review by the Division at this time. We will take the completed reviews to the Executive Carcinogenicity Assessment Committee (ECAC). The ECAC will determine if these studies are adequate.

General comments:

1. It would have been helpful to have prior concurrence from the ECAC on carcinogenicity dose selection and design to avoid potential problems with design and adequacy.

2. The Division should have been consulted prior to the early termination of any groups in carcinogenicity studies.

3. Pending ECAC review, completion of histopathological examination of all tissues for all animals might be required for lower dose(s) in the mouse and/or rat carcinogenicity studies.

The Division indicated that Sepracor's mouse and rat carcinogenicity studies will be taken to the ECAC in 1-2 months. Upon request, the minutes of the ECAC meeting can be made available.

Question 10.
Does the Agency concur that a systemic exposure-based NOAEL has been established for the 3 and 9 month inhalation toxicology studies with dogs, and that they are

adequate to characterize the chronic toxicity of arformoterol and support the NDA review and potential approval (pending review)?

Response:
Comments during the February 9, 2004 meeting were in the context of characterizing the toxicity of the degradant, desformoterol. ECG findings in dogs from the 13-week and 9-month toxicology studies were attributed to pharmacological effects of arformoterol. The dog is known to be highly sensitive to these effects of β2-adrenergic agonists.

There were concerns that the background of these formoterol effects in dogs could interfere with characterizing the toxicity of desformoterol. Further, the submitted dog study using desformoterol spiked into formoterol was limited to a single dose to characterize the toxicity of this degradant.

We cannot concur that NOAELs were identified in the 13-week and 9-month toxicology studies with dogs on the basis of the exposure-based risk assessment described in Amendment #356. From reviews of these studies, it appeared that ECG recordings were limited to 3-5 min/time point and it is possible that treatment-related ECG abnormalities could have been missed given the extent of monitoring.

However, from a nonclinical toxicology perspective, given that these findings are expected effects of a β2-adrenergic agonist in dogs, they would not appear to affect the review or potential approval of the NDA.

Question 11.
The toxicology studies performed with arformoterol are outlined in Appendix B and discussed in Section 5.2.2. Does the Agency agree that the toxicology program is complete and adequate to support the review and potential approval (pending review) of the NDA?

Response:
Yes. Pending review, the toxicology program appears complete and adequate to support the review and potential approval of the NDA. As discussed under Question 9, the adequacy of carcinogenicity studies is pending ECAC review.

Question 12.
The CMC section of the NDA for Arformoterol Tartrate Inhalation Solution will provide stability data to support a proposal for refrigerated storage ⊏ ⊐ and room temperature storage ⊏ ⊐ This statement will require a desformoterol specification of ⊏ ⊐ The qualification program for desformoterol has included the evaluation of acute and repeat-dose toxicity, mutagenicity, and safety pharmacology endpoints. Studies were conducted with both desformoterol (isolated) and a target ⊏ ⊐ desformoterol in arformoterol (see Section 5.2.2.7). Does the Agency concur that the scope of these studies is adequate to provide sufficient information to qualify desformoterol and evaluate, upon consultation with the CMC reviewers, a proposed desformoterol specification at the ⊏ ⊐

b(4)

Response:
Pending review, the 90-day inhalation toxicology study with desformoterol in rats could qualify desformoterol — in the drug product. b(4)

From a CMC perspective, the acceptance criterion for a given impurity/degradant is not set solely on its qualification level, but is also based upon its observed levels in the drug product at the proposed expiration dating period. Thus, if the drug product stability data show — desformoterol, the proposed acceptance criterion for desformoterol may be justified and allowed. b(4)

Question 13.
All nonclinical DM/PK studies performed with arformoterol are outlined in Tables D-G of Appendix B. Does the Agency agree that the nonclinical DM/PK program is complete and adequate to support the NDA review and potential approval (pending review)?

Response:
Pending review, the DM/PK program appears to be complete and adequate to support the NDA review and potential approval.

Additional Comment:
The issue of breaking the treatment blinds for some patients in the pivotal studies is not closed. Provide a convincing case with detailed substantiation that the studies were not compromised.

We are looking for a detailed explanation of the course of events, i.e., a step-by-step, day-by-day sequence of events.

The Division agreed with Sepracor to place the report of the blind-breaking events in an appendix to Section 8, with hyperlinks to the report from the applicable studies.

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

Akilah Green
Regulatory Project Manager

Drafted by:	Green/March 15, 2005
Initialed:	Sun/March 16, 2005
	Robison/March 16, 2005
	Starke/March 17, 2005
	Gunkel/March 17, 2005
	Wang/March 18, 2005
	Guo/March 18, 2005
	Fadiran/March 21, 2005
	Kim, S./March 21, 2005
	Chowdhury/Marc 25, 2005
Finalized:	Green/March 28, 2005

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
3/28/05 10:42:32 AM

MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 6, 2001

IND: 55,302 (r-r-formoterol)

SPONSOR: Sepracor

TYPE OF MEETING: In-person Meeting; End of Phase 2; IMTS 7519

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

Raymond Anthracite, M.D., Medical Reviewer
Young-Moon Choi, Ph.D., Clinical Pharmacology Reviewer
Eric Duffy, Ph.D., Division Director, DNDC II
Emmanuel Fadiran, Ph,D, Clinical Pharmacology Team Leader
Marianne Mann, M.D., Deputy Division Director
Timothy McGovern, Ph.D., Acting Pharmacology/Toxicology Team Leader
Robert J. Meyer, M.D., Division Director
Craig Ostroff, Pharm.D., Project Manager
Guirag Poochikian, Ph.D,. Chemistry Team Leader
Tim Robison, Ph.D., Pharmacology /Toxicology Reviewer
Vibhakar Shah, Ph.D., Chemistry Reviewer

SEPRACOR ATTENDEES:

Craig Abolin, Associate Director, Drug Metabolism
Paul Alessandro, Director, Regulatory Affairs
David Amato, Director, Biostatistics
Rudolf Baumgartner, Senior Director, Medical Operations
Joseph Boccagno, Senior Director, Clinical Project Management
Sarah Hlavachek, Senior Regulatory Affairs Associate
William McVicar, Executive Program Director
Gary Maier, Senior Director, Clinical Pharmacology
Prabu Nambiar, Director, Technical Regulatory Affairs
Jules Selden, Associate Director, Toxicology
Louis Vaickus, M.D., Vice President, Medical Operations
Chris Viau, Vice President, Preclinical Development
James Wachholz, Executive Director, Regulatory Affairs
Steve Wald, Senior Vice President, Chemical R&D
Tom Wilson, Director, Quality Control

BACKGROUND

Sepracor submitted a meeting request on July 3, 2001 (SN 040). Their briefing package was submitted on August 7, 2001, (SN 042) The sponsor is planning on submitting an NDA for this product within the next few years.

MEETING DISCUSSION

The overheads presented during the meeting are attached to the end of this document. The comments below are **in addition** to their content and should be used as a companion document to the attached slides. The questions posed by the sponsor are also restated in the attached slides. Comments by the Division are in regular font and those of the sponsor in *italics*.

Pharmacology/ Toxicology

The overheads were presented as attached.

Clinical Pharmacology

In general, the sponsor's overall approach and concepts are fine.

Question 1:

What are the responsible enzyme(s) for (R,R)-formoterol's (RR-F) formation?

The sponsor plans to investigate this area. It appears that the result may be consistent with the racemic data.

Conjugation is the proposed mechanism and we would require documentation of these results.

Question 2:

No additional comments.

Question 3:

The sponsor should investigate the protein binding of (R,R)-formoterol at therapeutic concentration.

Question 4:

If it is discovered from in-vitro metabolism studies that (R,R)-formoterol is metabolized by CYP2D6 it is recommended that the sponsor should perform a genotype study and perform a PK study of (R,R)-formoterol in CYP2D6 poor metabolizers.

The evaluation of the potential for chiral conversion could be done via adequate evaluation in healthy volunteers or in COPD patients. Study 016 should look into using a chiral method with the single-dose population. The division prefers to see the single and multiple dose PK done in the COPD patients.

The division stated that if the isomers of (R,R)-formoterol are not detected in plasma after a reasonable effort, measurement of (R,R)-formoterol in urine using a stereospecific assay would be acceptable.

Clinical:

Question 1:

It is likely that a waiver would be granted, but a decision cannot be made at this time.

Question 2:

An insufficient amount of information (e.g. only include background information on 22 patients) has been provided in the End of Phase 2 package to answer this question.

Question 3:

The division stated that the patient population studied in the Phase 3 trials becomes part of the indication for the drug. It was also noted that COPD patients who show reversibility might see a benefit without having a change in FEV1. Phase 3 testing is seen as confirmatory testing for results seen in Phase 2. Phase 3 is not typically a time when dose finding should take place.

Question 4:

No additional comments.

Question 5:
The division added that additional serial spirometry would also be needed to characterize the response over 24 hours for a QD dosing regimen claim.

The sponsor stated that study 091-052 would already meet that requirement.

The division responded that the number of patients was not large enough for a key phase 3 trial and that more spirometry data are generally needed for phase 3 trials.

The division suggested adding additional (spirometry) time points in at least one trial of 8, 12, 18 and 24 hours post dosing. This would be the minimum timepoints for spirometry necessary to support a claim of QD dosing. The 0-6 hour data currently captured along with the proposed phase 3 trial designs would only support QID dosing.

The division stated that the primary clinical endpoint proposed by the sponsor of peak % FEV1 would not be acceptable for maintenance therapy of a bronchodilator, as it did not characterize the action of the drug (i.e. bronchodilation) over the entire dosing interval. The division stated that a more acceptable endpoint would be FEV_1 measured over time (i.e. FEV_1 AUC_{0-24}).

The division inquired as to why the sponsor [ ] b(4)

[ ]

[ ] b(4)

The division also inquired into why the sponsor switched from the 3-ml vial to the 2-ml vial?

The sponsor replied that this switch was motivated by their desire to reduce nebulization time and thus potentially improve compliance with therapy.

Question 6:

No additional comments

Question 7:

[ ] b(4)

The division stated that the label warnings for short-onset, long-acting bronchodilators are likely to be different than those for long-acting bronchodilators with a slower onset of action.

The division suggested that a side-by-side comparison of the Serevent and Foradil labels might clarify the issue of acute-use for the sponsor.

Question 8:

No additional comments.

Question 9:

No additional comments.

Question 10:

No additional comments.

[An additional discussion took place concerning the doses studied by the sponsor and the safety profile of (R,R)-formoterol]

The sponsor needs to look at the safety profile closely to assure that the ultimate risk:benefit of the product is acceptable. There is a trade-off of safety to efficacy that could be a review issue.

Based upon the 091-021 COPD study and the 2-ml vial use, the safety profile of (R,R)-formoterol at the doses proposed for the phase 3 studies cannot be predicted. Additional dose-ranging studies with clinically relevant endpoints are recommended, including the determination of a no-effect dose. The division stated that the proposed doses may be at the high end of the dose response curve and that the risk was that if safety signals were observed at the lowest proposed dose – the entire program could be in jeopardy.

The safety parameters proposed for the phase 3 program generally were acceptable but Holter studies, Glucose and Potassium levels needed to be tested more often (i.e pre-dose; post-dose at every visit).

The sponsor presented the slides as attached. This included safety and efficacy data from studies 091-021 COPD and 091-004 asthma. They summarized the safety controls in the phase 3 studies, including the use of a Data Safety Monitoring Board. These included FEV1, Glucose, K, Troponin, CK-MB, Cardiac events, Adverse Events. For study 091-004 they include Adverse events, K (start and at day 21), Nocturnal awakenings, heart rates.

The division stated that it appeared that adequate safety controls were being planned for the phase 3 program but they would be addressed and reviewed when the full study protocols were submitted to the division and as an NDA review issue.

The division inquired as to the type of nebulizer to be used in the phase 3 program.

The sponsor indicated that they would use a single nebulizer (the PARI LC PLUS) across all of the centers in the phase 3 program.

The division responded that the label would reflect this fact (i.e. the type of nebulizer used) and may include language such as, that the safety and efficacy of (R,R)-formoterol delivered by other nebulizers had not been established.

26 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 8

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

/s/

Craig Ostroff
7/19/02 04:59:24 PM

MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 6, 2001

IND: 55,302 (r-r-formoterol)

SPONSOR: Sepracor

TYPE OF MEETING: In-person Meeting; End of Phase 2: CMC; IMTS 8793

FDA ATTENDEES:

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

Craig Ostroff, Pharm.D., Project Manager
Guirag Poochikian, Ph.D,. Chemistry Team Leader
Vibhakar Shah, Ph.D., Chemistry Reviewer

SEPRACOR ATTENDEES:

Paul Alessandro, Director, Regulatory Affairs
Joseph Boccagno, Senior Director, Clinical Project Management
Sarah Hlavachek, Senior Regulatory Affairs Associate
William McVicar, Executive Program Director
Prabu Nambiar, Director, Technical Regulatory Affairs
James Wachholz, Executive Director, Regulatory Affairs
Steve Wald, Senior Vice President, Chemical R&D
Tom Wilson, Director, Quality Control

BACKGROUND

Sepracor submitted a meeting request on July 3, 2001 (SN 040). Their briefing package was submitted on August 7, 2001 (SN 042) The sponsor is planning on submitting an NDA for this product within the next few years. The End of Phase 2 meeting concerning the nonclinical and clinical disciplines was held on the morning of September 6, 2001.

MEETING DISCUSSION

The overheads presented during the meeting are attached to the end of this document. The comments below are **in addition** to their content. Comments by the Division are in regular font and those of the sponsor in *italics*.

Question 1
The sponsor should address stereoisomers in their development work and at NDA filing describe how you are controlling for process impurities.

Question 2 & 3

b(4)

Questions 4 & 5

No additional comments.

Question 6

b(4)

b(4)

The division also indicated that to increase the legibility of the embossed information on the vial, a larger tab portion of the vial would be preferable. The product name, strength, lot number, amount and expiry would all have to be legibly arranged on the tab. Additionally, paper labels are an option, but the volatile components of the inks and adhesives are issues of concern that would have to be properly addressed. An overwrap could also be considered in this situation. The division is open to further discussion on this issue with the sponsor.

Question 7

b(4)

The sponsor stated that levels of ⊏ ⊐ *were seen after* ⊏ ⊐ *of storage under refrigerated conditions.*

The division stated that the stability data generated should determine the specifications that you set for the drug product and that the sponsor should set a ceiling for the ⊏ ⊐

b(4)

Question 8

No additional comments.

10 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 9

ACTION PACKAGE CHECKLIST

Application Information

BLA # / NDA # 21-912	BLA STN# / NDA Supplement #	If NDA, Efficacy Supplement Type
Proprietary Name: Brovana Established Name: arformoterol tartrate Dosage Form: Inhalation Solution		Applicant: Sepracor
RPM: Ladan Jafari		Division: Pulmonary and Allergy / Phone # 301-796-1231

NDAs:
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)

505(b)(2) NDAs and 505(b)(2) NDA supplements:
Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ If no listed drug, check here and explain:

Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.

☐ Confirmed ☐ Corrected
Date:

❖ User Fee Goal Date ❖ Action Goal Date (if different)	October 12, 2006 O
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)*	☒ Requested in AP letter ☐ Received and reviewed

❖ Application Characteristics

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

NDAs, BLAs and Supplements:
☐ Fast Track
☐ Rolling Review
☐ CMA Pilot 1
☐ CMA Pilot 2

☐ Orphan drug designation

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

NDAs and NDA Supplements:
☐ OTC drug

Other:

Other comments:

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP	☐ Yes ☒ No
• Exception for review *(file Center Director's memo in* Administrative Documents *section)*	☐ Yes ☐ No
• OC clearance for approval *(file communication in* Administrative Documents *section)*	☐ Yes ☐ Not an AP action
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

❖ Exclusivity	
• NDAs: Exclusivity Summary (approvals only) *(file Summary in* Administrative Documents *section)*	☒ Included
• Is approval of this application blocked by any type of exclusivity?	☐ No ☒ Yes
• NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic 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.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• NDAS: Is there remaining 5-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 ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: 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 ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 6-month pediatric 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 ☐ Yes If yes, NDA # and date exclusivity expires:
❖ Patent Information (NDAs and NDA supplements only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• 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) ☐ Verified 21 CFR 314.50(i)(1) ☐ (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).	☐ No paragraph III certification Date patent will expire
• [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 section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ 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	☐ Yes ☐ No

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)? ☐ 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 section below (*Summary Reviews*).*

*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? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) 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 section below (*Summary Reviews*).*

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

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) 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 section below (*Summary Reviews*).* *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.*	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) *(indicate date for each review)*	October 6, 2006
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) *(indicate date)*	
Labeling	
❖ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	October 4, 2006
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	October 4, 2006
• Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	December 8, 2005
❖ Patient Package Insert	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	October 4, 2006
• Original applicant-proposed labeling	December 8, 2005
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (**full color** carton and immediate-container labels)	
• Most-recent division-proposed labels (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	October 5, 2006
❖ Labeling reviews and minutes of any labeling meetings *(indicate dates of reviews and meetings)*	☒ DMETS 10/2/06, 8/28/06, 6/27/06, ☒ DSRCS 9/14/06, 6/1/06 ☒ DDMAC 8/2/06 ☐ SEALD ☐ Other reviews ☐ Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) *(indicate date of each review)*	3/1/06
❖ NDA and NDA supplement approvals only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ AIP-related documents • Center Director's Exception for Review memo • If AP: OC clearance for approval	 N/A N/A
❖ Pediatric Page (all actions)	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. *(Include certification.)*	☒ Verified, statement is acceptable
❖ Postmarketing Commitment Studies	☐ None
• Outgoing Agency request for post-marketing commitments *(if located elsewhere in package, state where located)*	10/2/06
• Incoming submission documenting commitment	10/5/06
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	See all documents attached.
❖ Internal memoranda, telecons, email, etc.	
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	N/A
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg 3/28/05
• EOP2 meeting *(indicate date)*	☐ No mtg 9/6/01
• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting	☒ No AC meeting
• Date of Meeting	
• 48-hour alert or minutes, if available	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	

CMC/Product Quality Information	
❖ CMC/Product review(s) *(indicate date for each review)*	9/29/06, 9/21/06, 8/23/06, 6/15/06
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer *(indicate date for each review)*	☒ None
❖ BLAs: Product subject to lot release (APs only)	☐ Yes ☐ No
❖ Environmental Assessment (check one) (original and supplemental applications)	
• ☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	8/23/06
• ☐ Review & FONSI *(indicate date of review)*	
• ☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) *(indicate date of each review)*	7/12/06 ☐ Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: 7/03/06 ☒ Acceptable ☐ Withhold recommendation

❖ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and supplemental applications) *(indicate date completed, must be within 60 days prior to AP)*	☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☐ Completed ☒ Requested ☐ Not yet requested ☐ Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	8/24/06, 8/3/06, 6/7/06
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc 6/2/06, 5/24/06
❖ ECAC/CAC report/memo of meeting	6/15/06
❖ Nonclinical inspection review Summary (DSI)	☒ None requested
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	9/1/06, 2/14/06
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	9/1/06
❖ Clinical consult reviews from other review disciplines/divisions/Centers *(indicate date of each review)*	☒ None
❖ Microbiology (efficacy) reviews(s) *(indicate date of each review)*	☒ Not needed
❖ Safety Update review(s) *(indicate location/date if incorporated into another review)*	9/1/06
❖ Risk Management Plan review(s) (including those by OSE) *(indicate location/date if incorporated into another review)*	
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date of each review)*	☐ Not needed
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☒ None requested
• Clinical Studies[1]	
• Bioequivalence Studies	
• Clin Pharm Studies	
❖ Statistical Review(s) *(indicate date for each review)*	☐ None 8/11/06, 2/22/06
❖ Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 9/7/06, 8/4/06, 2/10/06

Appendix A to Action Package Checklist

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

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a writt right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.

(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.

(3) **Or** 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.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).

(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.

(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).

(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.

(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.