CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-837

CORRESPONDENCE

TEAM LEADER MEMORANDUM

TO: NDA 20-837
THROUGH: John K. Jenkins, MD
FROM: Peter K Honig, MD
RE: Levalbuterol (Xopenex®)
DATE: May 26, 1998

/S/ 5/26/98

/S/ 5/11/98

Background:

Levalbuterol is the R-enantiomer of albuterol and, like the racemate, is a relatively selective B-2 agonist. Preclinical and clinical data suggest that the beneficial effects of albuterol is due to the R-enantiomer and little therapeutic benefit is conferred by the S-enantiomer. Other data implicate that the S-enantiomer may be functioning as more than just enantiomeric ballast and, in fact, be responsible for enhanced bronchial hyperreactivity. Sepracor has developed levalbuterol solution as a bronchodilator to be administered by nebulization in an effort to take advantage of these findings. Other dosing forms (e.g. MDI, tablet) are also under consideration for future development.

Clinical Pharmacology and Pharmacodynamic Studies:

Three methacholine challenge studies were conducted to evaluate the absolute and relative bronchoprotective effects of levalbuterol and racemic albuterol (Studies 001, 007 and 025). Significant protective effects were shown for levalbuterol at doses as low as 100 mcgs when methacholine challenges were conducted 20 minutes after drug administration. Higher doses of levalbuterol up to 1.25 mgs appeared to provide significant protection up to 3 hours and was comparable to the effect conferred by administration of 2.5 mgs of racemic nebulized albuterol.

Three clinical pharmacology studies (Studies 006, 008, and 021) evaluated the relative pharmacokinetics of levalbuterol and racemic albuterol in asthmatic patients. In general, the systemic availability of R-albuterol was more than twice that of the enantiomer. That is, the plasma levels of R-albuterol were higher after administration of levalbuterol than after those achieved after administration of a equivalent milligram dose of the racemic mixture. The adverse event profile was consistent with this finding.

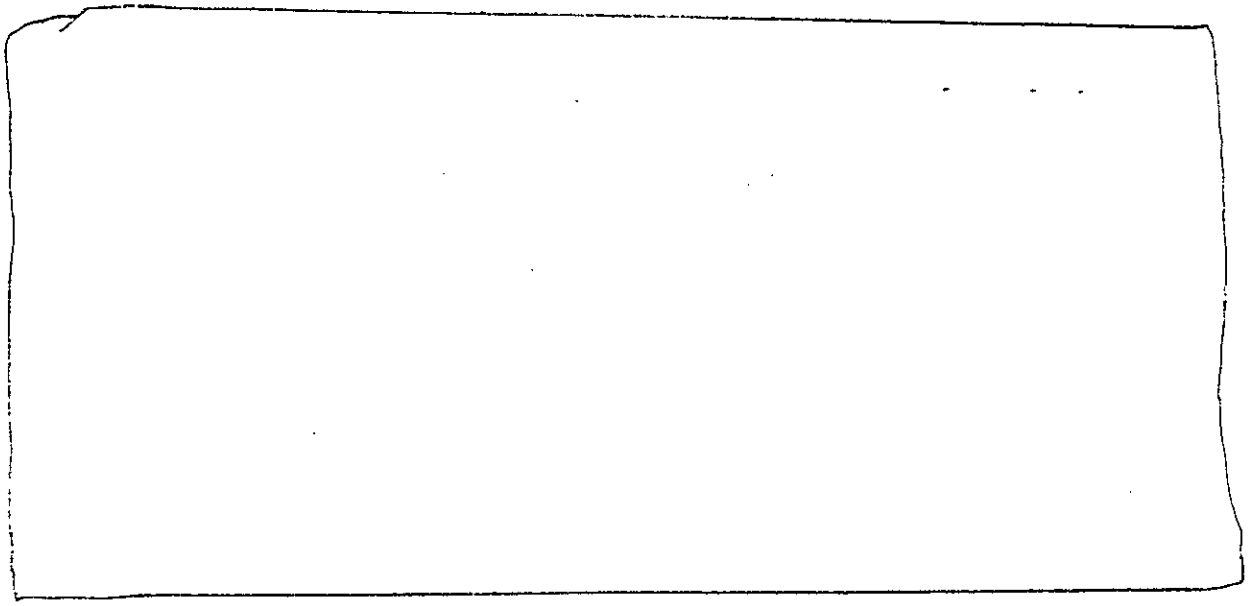
Clinical Efficacy Studies:

The sponsor conducted three safety and efficacy trials (Studies 005, [redacted] and 024) in asthmatic patients. Two of these studies evaluated adult patients. The first, Study 005, was a randomized, double-blind, placebo-controlled, single-dose, crossover trial evaluating the dose response of levalbuterol in twenty mild to moderate asthmatic patients. Doses of 0.31 mgs, 0.63 mgs, 1.25 mgs of levalbuterol were compared to 2.5 mgs of racemic albuterol and placebo. The results demonstrated a dose-response

trend for the three doses of levalbuterol for the endpoint of mean percent change from baseline in FEV1; however, no statistically significant differences between dose were observed. Numerically, the 0.63 mg dose of levalbuterol and 2.5 mg dose of racemic albuterol provided comparable differences from placebo. There were no meaningful differences in onset of action (i.e. time to reach 15% improvement in FEV1) between any of the active treatments. The duration of activity (time from onset to when FEV1 fell below a 15% improvement from baseline) demonstrated dose-ordering for levalbuterol with the 1.25 mg dose having a mean duration of >250 minutes. Safety parameters including vital signs and clinical laboratories (potassium and glucose) also showed a dose-response relationship for levalbuterol.

The second study in adults (Study 024) was a randomized, double-blind, placebo- and active-treatment controlled, repetitive-dose, 4-week study in 362 asthmatic patients. This study compared doses of 0.625 mgs and 1.25 mgs of levalbuterol with 1.25 mg and 2.5 mg of racemic albuterol and placebo all administered on a TID schedule. Serial FEV1s over the dosing interval were obtained after the first dose and after 2 and 4 weeks of treatment. The results indicated that a levalbuterol dose of 0.625 mgs provided comparable first-dose bronchodilatory effects (i.e. onset of action, peak effect, AUC, and duration of action) to that of 2.5 mgs of racemic albuterol. Significant bronchodilatation over the proposed 8-hour dosing interval was demonstrated for both the 0.625 mg and 1.25 mg doses of levalbuterol. After chronic dosing, the same degree of bronchodilatation was noted for both doses of levalbuterol. Interestingly, the pre-dose baseline at Week 4 was improved for both doses of levalbuterol (6-7%). This finding was not shown for the racemic albuterol treatment arms. The use of rescue medication was also greater in the patients who received racemic albuterol than in patients who received levalbuterol. Secondary endpoints such as nocturnal awakenings and symptom-free days indicated numerical superiority for the 1.25 mg dose of levalbuterol over the lower dose. The safety results from this study indicated a dose-response relationship for adrenergically-related adverse events for levalbuterol. The data also demonstrated a higher frequency of such events for the 1.25 milligram levalbuterol dose versus the 2.5 milligram racemic albuterol dose. This is consistent with the pharmacokinetic data from the clinical pharmacology studies. Since the 0.625 mg dose of levalbuterol produced the same degree of bronchodilatation as 2.5 mg of racemic albuterol solution, the lower dose of levalbuterol and the 8 hour dosing interval are appropriate. Since a dose of 1.25 mg of levalbuterol produced a greater degree of bronchodilatation and less rescue medication requirements than the lower dose, it is appropriate that this dose also be approved and recommended for use in more severe adult patients.

A center in this study was determined to have data integrity problems (Edwards site). These primarily consisted of altered source documents and was initially detected by the sponsor and confirmed by DSI. A reanalysis of the efficacy and safety data excluding this site was requested and submitted by the sponsor. No significant differences were noted.



Team Leader Recommendation:

Levalbuterol solution for nebulization should be approved for patients 12 years of age and older. Both the 0.63 mg and 1.25 mg dose should be approved for administration every 8 hours for the treatment of acute bronchospasm in patients with reversible airway obstruction. A prevention indication (i.e. EIB) is not supported by the available data. Levalbuterol should not be approved for patients below the age of 12 years. In order to support such an indication, the sponsor should conduct a

This recommendation was initially made at the EOP2 meeting and reiterated at the pre-NDA meeting with the sponsor. The proposed proprietary name, Xopenex®, is acceptable to the Labeling and Nomenclature Committee and this reviewer. Product labeling will be the focus of a separate review.

cc:
NDA20-837/Division File
HFD-570/MO/Nicklas/Honig
HFD-570/PM/Jani

APPEARS THIS WAY
ON ORIGINAL

Memorandum

To: NDA 20-837
From: Hilary V. Sheevers - Pharm./Tox. Team Leader /S/ 6/17/98
Re: Team Leader NDA Summary, HFD 570
Date: June 17, 1998

Overall Recommendation (Pharm/Tox): Approval/able

Xopenex is the inhalation solution formulation of the R-enantiomer of albuterol, a B2 agonist, intended for asthmatics ages 12 years and above; the proposed dosage is up to 3.75 mg/day in adults. As an enantiomer of a long-approved drug product, the sponsor complied to the needed studies described in the draft Stereoisomer Guidance document.

Outstanding Issues:

The sponsor has several impurities to qualify or reduce in concentration according to ICH guidelines. Outside of finalizing the label with the sponsor, there are no other outstanding pre-clinical issues at this time.

Summary of Significant Preclinical Studies:

A large set of preclinical studies have been performed for previously approved R;S albuterol drug products. Based on chemistry estimates, we assumed 50% of these previous products consisted of the single enantiomer, and the label dose-multiples for carcinogenicity etc. were based on this estimate. The sponsor submitted several pharmacology studies to compare the potency of R-albuterol to the racemic mixture. The single enantiomer was similar to the racemic mixture in binding beta adrenoreceptors in rat heart and pig lung tissues, although the single enantiomer was twice as potent in stimulating maximum cAMP levels.

The sponsor performed subchronic toxicity studies of R-albuterol in rats and dogs for 28 and 90 days. At high doses, increased mean heart rates and myocardial fibrosis in rats and dogs, as well as changes in the spleen (capsulitis, rats only) were noted. As noted previously for drugs of this class in chronic toxicity studies of the racemic mixture, cardiotoxicity appears as the major toxicity of concern. Other toxicities noted are generally related to exaggerated pharmacodynamic effects of beta agonists. The NOAEL for R-albuterol was estimated at 0.3 mg/kg, approximately 5-10 times the human adult dose.

Reproduction studies were performed in the rat to test impairment of fertility (Segment I) and multi-generational reproductive effects (Segment III), and in rats and rabbits to test for teratogenicity (Segment II) by other sponsors using the racemic mixture. The sponsor performed one rabbit teratology (Segment II) study using R-albuterol and the racemic mixture. No embryo or fetal toxicity was noted. Findings is earlier studies with the racemic mixture have shown albuterol to be teratogenic in mice and Stride Dutch rabbits. No changes have been noted in fertility or reproductive performance.

Carcinogenicity studies were completed by other sponsors of the racemic mixture. In rats, benign leimyomas were noted at doses near the clinical dose. This finding appears with most (perhaps all) beta agonists in this animal strain, and has been shown to be reversible by propranolol, a beta antagonist. Racemic albuterol was negative for tumorgenicity in mice and golden hamsters. All genotoxicity and mutagenicity studies were negative for albuterol, including two in vitro assays completed by the sponsor with R-albuterol.

The sponsor should qualify or lower the concentration of the impurities monoethyl ether albuterol to [redacted]% (based on ICH guidelines) and albuterol aldehyde to [redacted]% (based on safety data from other submissions).

CC: Division file, Jani, Whitehurst

MEMORANDUM

DATE: June 29, 1998 /S/ 6/29/98

FROM: John K. Jenkins, M.D.
Director, Division of Pulmonary Drug Products, HFD-570

TO: NDA 20-837

SUBJECT: Overview of NDA review issues

Administrative

NDA 20-837 for XOPENEX (levalbuterol hydrochloride) Inhalation Solution was submitted by Sepracor, Inc. on July 1, 1997. Levalbuterol is the R-enantiomer of the currently marketed racemic of albuterol. The application was reviewed by the Division as a standard (i.e., non-priority) application. Information request letters related to numerous CMC deficiencies were issued to the sponsor on May 4 and 20, 1998. To date, the sponsor has not submitted a complete response to these requests. The current user fee goal date for this application is July 1, 1998.

Clinical

As noted above, levalbuterol is the R-enantiomer of racemic albuterol. The proposed formulation is a solution for inhalation using a jet nebulizer. The proposed indication is for the treatment or prevention of [redacted] bronchospasm in patients [redacted] years of age and older with reversible obstructive airway disease. In support of the proposed indication, the sponsor submitted the results of three methacholine challenge studies, three clinical pharmacology studies, and three safety and efficacy studies in adults and children (Studies 005, [redacted] and 024). For a more detailed review of the clinical database submitted to this application, please refer to the Medical Officer Review prepared by Dr. Nicklas and the Medical Team Leader Memorandum prepared by Dr. Honig.

Study 005 was designed to compare several doses of levalbuterol (0.3125, 0.625, and 1.25 mg) to racemic albuterol (2.5 mg) in adult patients with mild to moderate asthma. This study demonstrated a dose-response trend for the three doses of levalbuterol for mean percent change from baseline for FEV_1, however, no statistically significant differences were observed between the three doses. Generally the 1.25 mg dose of levalbuterol was most comparable to the 2.5 mg dose of racemic albuterol when all efficacy endpoints were considered, e.g., time to onset, peak effect, duration of effect, etc. This finding provides support to the sponsor's hypothesis that the R-enantiomer is primarily responsible for the bronchodilation observed following administration of racemic albuterol. With regard to safety, while there were no statistically significant differences for any safety outcome between levalbuterol 1.25 mg and racemic albuterol 2.5 mg, a numerical trend for several safety endpoints suggested more systemic adverse events with the 1.25 mg levalbuterol dose. This finding is consistent with the pharmacokinetic studies, which demonstrated that systemic exposure to R-albuterol was

greater following administration of 1.25 mg levalbuterol compared to 2.5 mg racemic albuterol.

Study 024 was a randomized, double-blind, placebo- and active-controlled, 4-week trial in patients 12 years of age and older with moderate to severe asthma. The active dose levels included in this trial were 0.625 and 1.25 mg of levalbuterol and 1.25 and 2.5 mg of racemic albuterol administered on a three times a day schedule. (Note: The dosing recommendations for racemic albuterol solution are 2.5 mg three or four times daily for adults and children 12 years of age and older.) Overall the results of this study clearly demonstrated the efficacy of levalbuterol at doses of 0.625 and 1.25 mg three times daily. Perhaps somewhat surprisingly, levalbuterol at a dose of 0.625 mg was generally clinically comparable on most efficacy parameters to racemic albuterol at a dose of 2.5 mg. Levalbuterol at a dose of 1.25 mg generally resulted in slightly greater degrees of bronchodilation than either the 0.625 mg dose of levalbuterol or the 2.5 mg dose of racemic albuterol. As noted by Drs. Honig and Nicklas, on chronic dosing there was a slight improvement (6-7%) in the pre-dose baseline FEV_1 for both levalbuterol doses. Such an improvement in the pre-dose baseline was not observed for the racemic albuterol or placebo groups. While interesting in light of the sponsor's hypothesis that [redacted] this finding is not adequate to support any claim of such a benefit that may be clinically meaningful following long-term use of levalbuterol. The safety data from this study generally confirmed the trend toward an increased incidence of systemic adverse effects for the 1.25 mg dose of levalbuterol seen in study 005 (see above). Again, this finding is likely related to the higher systemic exposure to R-albuterol seen following administration of levalbuterol. I concur with Drs. Nicklas and Honig that the results of Study 024 support a usual dosing recommendation of 0.625 mg for levalbuterol. The 1.25 mg dose of levalbuterol is also approvable, but should be reserved for patients in whom the 0.625 mg dose is not optimally effective and where the risk of increased systemic adverse reactions is justified by the potential for increased efficacy.

[redacted]

[redacted]

This application is clinically approvable for relief of bronchospasm in patients 12 years of age and older provided the draft package insert is adequately revised to reflect the Division's review of the clinical data. Additional studies will be required to support approval of the proposed pediatric and prevention indications. Preliminary labeling comments will be provided to the sponsor with the action letter.

Pharmacology/Toxicology

The sponsor followed the recommendations contained in the Stereoisomer Guidance document in conducting the pre-clinical studies to support this application. Please refer to the Pharmacology/Toxicology review prepared by Dr. Whitehurst and to the Pharmacology/Toxicology Team Leader Memorandum prepared by Dr. Sheevers for more complete details of the results of the studies. The sponsor conducted a 28-day toxicity study in rats and 90 days studies in both rats and dogs with levalbuterol. Overall, these studies demonstrated that the toxicity of levalbuterol and racemic albuterol are similar in animals. The primary outstanding issue is for the sponsor to adopt specifications for impurities/degradation products that are acceptable based on ICH guidelines and the safety margins for these compounds. Of particular concern is the proposed limit for albuterol aldehyde which much be significantly reduced consistent with the levels the Division has allowed in other recently approved applications.

The application is approvable from a pharmacology/toxicology standpoint with acceptable labeling and pending resolution of the specifications for impurities and degradation products. Preliminary labeling comments will be included in the action letter.

Biopharmaceutics and Clinical Pharmacology

Please refer to the review prepared by Dr. Gillespie for a complete review of the biopharmaceutics and clinical pharmacology data submitted in support of this application. The primary finding from the clinical pharmacology studies is that the systemic exposure to R-albuterol following administration of levalbuterol is 1.5 to 2.0 times higher than that seen following administration of racemic albuterol at twice the nominal dose. This was a somewhat unexpected finding, however, it was confirmed by the fact that more systemic adverse events were noted in clinical trials in patients that received levalbuterol 1.25 mg as compared to patients who received racemic albuterol 2.5 mg. The cause of the increased systemic exposure is not known. As noted above in the Clinical section, the increased systemic exposure and the increased rate of occurrence of systemic adverse effects leads to a conclusion that the 1.25 mg dose of levalbuterol should be reserved for patients who do not respond adequately to 0.625 mg and in whom the increased risk of systemic adverse events is favorably balanced by the increased benefit from the higher dose. The primary outstanding issue at this point besides labeling is the question of whether inter-conversion from the R-form to the S-form of albuterol occurs in-vivo when

levalbuterol is administered. This question is raised due to the observation that one subject who received S-albuterol was found to have R-albuterol in plasma samples. The sponsor will be asked to explain this finding.

The application is approvable from a biopharmaceutics and clinical pharmacology standpoint with acceptable labeling and provided the sponsor can adequately address the issue of whether inter-conversion occurs in vivo.

Chemistry, Manufacturing, and Controls

The proposed product is a solution for inhalation and the sponsor proposes to market three strengths (0.625, and 1.25 mg) in 3-ml unit-dose LDPE vials. The vials will be wrapped in a foil laminate protective pouch. As note above, the sponsor received IR letters dated May 4 and 20, 1998, that listed numerous CMC deficiencies. The sponsor submitted a response to these IR letters on May 29, 1998. The Division has reviewed the sponsor's response to the IR letters and has determined that the response is not complete, therefore, the submission was accepted as correspondence and will not be reviewed prior to the issuance of the action letter.

The application is not approvable from a CMC standpoint. The deficiencies noted in the IR letter will be restated in the action letter.

Data Integrity

The Division of Scientific Investigations conducted audits of four of the clinical sites that participated in the pivotal clinical trials for this application. Two of the sites were rated as NAI, one site was rated VAI due to minor deficiencies, and one site was rate OAI due to major deficiencies. The OAI-rated site was that of Dr. Edwards who participated in Study 024. Both the sponsor and the DSI auditors noted serious deficiencies at this site including alteration of source documents. The sponsor was asked to reanalyze the results of Study 024 excluding Dr. Edwards' site and no significant differences in the study outcomes were noted. Given the lack of significant findings at the other three sites, it is reasonable to conclude that Dr. Edwards' site was unique and that the overall integrity of the clinical trials database is preserved. The depiction of the efficacy data from Study 024 in the labeling should exclude the data from Dr. Edwards' site.

Labeling

The proposed tradename "Xopenex" has been reviewed by the LNC and the Division as is acceptable to both. Earlier versions of the tradename, and were found to be similar in spelling and/or sound to other approved drugs and were deemed unacceptable due to concerns regarding potential prescribing and dispensing errors. The sponsor will be provided with preliminary labeling comments in the action letter. Final labeling negotiations will be deferred pending resolution of outstanding issues noted above.

Recommendation

There are numerous outstanding CMC deficiencies that must be corrected prior to approval of this application. Given that the application is generally approvable, albeit with a more restricted indication than proposed by the sponsor, with acceptable labeling with regard to other disciplines, the sponsor should receive an APPROVABLE letter. Preliminary labeling comments will be included with the action letter.

cc:
NDA 20-837
HFD-570/Division File
HFD-570/Jenkins
HFD-570/Honig
HFD-570/Jani

Jani

NDA 20-837

OCT 7 1998

Sepracor Inc.
111 Locke Drive
Marlborough, Massachusetts 01752

Attention: James Wachholz
Senior Director, Regulatory Affairs

Dear Mr. Wachholz:

We acknowledge receipt on September 25, 1998, of your September 24, 1998, resubmission to your new drug application (NDA) for Xopenex (levalbuterol hydrochloride) Inhalation Solution.

This resubmission contains additional information submitted in response to our July 1, 1998, action letter and our facsimile transmission dated August 31, 1998.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is March 25, 1999.

If you have any questions, contact Parinda Jani, Project Manager, at (301) 827-1064.

Sincerely yours,

Cathie Schumaker, R.Ph.
Chief, Project Management Staff
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

HFD-570/P. JANI

JUL - 1 1998

NDA 20-837

Sepracor Inc.
111 Locke Drive
Marlborough, Massachusetts 01752

Attention: Pauliana C. Hall, R.A.C.
Vice President, Regulatory Affairs

Dear Ms. Hall:

Please refer to your pending new drug application dated June 30, 1997, received July 1, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xopenex (levalbuterol hydrochloride) Inhalation Solution.

We acknowledge receipt of your submissions dated August 4, September 8 and 17, October 21, November 4 and 20, and December 1, 1997, and April 9, 1998. The user fee goal date for this application is July 1, 1998.

We also acknowledge receipt of your submission dated May 29, 1998. Please be advised that this submission has been accepted as correspondence and has not been reviewed prior to issuance of this letter.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before this application may be approved, however, a satisfactory inspection of [redacted] will be required. In addition, it will be necessary for you to address the following deficiencies.

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Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application. Any amendments should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or teleconference with the Division to discuss what further steps need to be taken before the application may be approved.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please contact Ms. Parinda Jani, Project Manager, at (301) 827-1064.

Sincerely yours,

John K. Jenkins, M.D., F.C.C.P.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Attachment

26 **Page(s) Redacted**

Draft

Labeling

NDA 20-837

MAY 20 1998

Sepracor Inc.
111 Locke Drive
Marlborough, Massachusetts 01752

Attention: Pauliana C. Hall, R.A.C.
Vice President, Regulatory Affairs

Dear Ms. Hall:

Please refer to your pending new drug application dated June 30, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xopenex (levalbuterol hydrochloride) Inhalation Solution.

We also refer to your amendments dated August 4, and October 21, 1997.

We have completed our review of the chemistry, manufacturing and controls (CMC) section of your submission and have identified the following deficiencies.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments have been reviewed only to the level of the discipline team leader. They do not reflect division director input or concurrence and should not be construed to do so. These comments are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you respond in the current review cycle, we may or may not consider your response prior to taking an action on your application. In the meantime, we are continuing our review of your application.

If you have any questions, please contact Ms. Parinda Jani, Project Manager, at (301) 827-1064.

Sincerely yours,

Guirag Poochikian, Ph.D.
Chemistry Team Leader, DNDC II
Division of Pulmonary Drug Products (HFD-570)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Farinda.

NDA 20-837

MAY - 4 1998

Sepracor Inc.
111 Locke Drive
Marlborough, Massachusetts 01752

Attention: Pauliana C. Hall, R.A.C.
Vice President, Regulatory Affairs

Dear Ms. Hall:

Please refer to your pending new drug application dated June 30, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zopen (levalbuterol hydrochloride) Inhalation Solution.

We also refer to your amendments dated August 4, and October 21, 1997.

We have completed our review of the chemistry, manufacturing and controls (CMC) section of your submission and have identified the following deficiencies.

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We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments have been reviewed only to the level of the discipline team leader. They do not reflect division director input or concurrence and should not be construed to do so. These comments are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you respond in the current review cycle, we may or may not consider your response prior to taking an action on your application. In the meantime, we are continuing our review of your application.

If you have any questions, please contact Ms. Parinda Jani, Project Manager, at (301) 827-1064.

Sincerely yours,

Guirag Poochikian, Ph.D.
Chemistry Team Leader, DNDC II
Division of Pulmonary Drug Products (HFD-570)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

17 **Page(s) Redacted**

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Labeling

Memorandum of Telephone Facsimile Correspondence

Date: February 22, 1999

To: James Wachholz
Regulatory Affairs

From: Parinda Jani
Project Manager

Through: John K. Jenkins, M.D., F.C.C.P. /S/ 2/24/99
Division Director

Subject: Labeling Comments for NDA 20-837/Xopenex Inhalation Solution

We are providing the attached labeling comments via telephone facsimile for your convenience, to expedite the progress of your drug development program. Please note that these comments are PRELIMINARY. The labeling comments for the carton and containers will be sent to you at a later on date.

Thank you.

APPEARS THIS WAY ON ORIGINAL

22 **Page(s) Redacted**

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Labeling

Minutes of Teleconference

MAR 22 1999

NDA: 20-837 **Date:** March 19, 1999
Sponsor: Sepracor Inc.
Product: Xopenex (levalbuterol HCl) Inhalation Solution, 0.63 mg/3 mL, 1.25 mg/3 mL
FDA Attendees: Jani, Poochikian, Shah
Sepracor Attendees: Donovan, Mueller, Prabhakar, Wachholz, Wald, Wilson

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Background: A FAX was sent to the sponsor on March 15, 1999, listing CMC deficiencies that needed to be resolved before the approval of this NDA. The Agency provided clarification in a teleconference on March 16, 1999. Sepracor submitted its response on March 18, 1999, in which as requested by the Agency, several specifications were tightened (see attached revised drug product specifications sheet), and additional stability data were presented. Upon review of these data, it was determined that the proposed storage temperature and expiration dating period were inappropriate. This teleconference was scheduled to inform Sepracor of appropriate storage temperature/expiration dating period for this product.

The Agency stated that based on the available stability data, the proposed expiration dating period of [redacted] months at room temperature ($15^0C - 25^0C$) is not supportive. The Agency offered Sepracor options of either storage at room temperature with shorter expiration dating period, or, [redacted] months of expiration dating period under refrigeration storage. The Agency and Sepracor agreed to the following:

- The recommended storage for this product will be at room temperature with expiration dating period of 15 months for 0.63 mg/3mL vials, and 12 months for 1.25 mg/3 mL vials.
- In future, Sepracor can [redacted] through a "Prior Approval" supplement.

/S/

Parinda Jani
Project Manager

APPEARS THIS WAY
ON ORIGINAL

CC:
ORIG NDA 20-837
DIV FILE/HFD-570
HFD-570/JANI/3-22-99
HFD-570/SHAH
HFD-570/POOCHIKIAN

Jan 1

MEMORANDUM OF TELEPHONE CONVERSATION

Date: November 30, 1998

Between: John K. Jenkins, M.D. /S/ 11/30/98

And

Dave Barlow, Sepracor

Subject: Xopenex NDA 20-837 Review Status

Mr. Barlow called me today and I later returned his call.

Mr. Barlow inquired as to the status of the review of the Xopenex NDA and what his company could do to expedite the review process at this point. I explained to Mr. Barlow that the application was currently under review and that the PDUFA goal date was March 25, 1999. I assured him that we would complete our reviews and issue an action letter by the PDUFA goal date. I informed him that the various disciplines involved in the review will be completing their review of the application as their workload and other deadlines permit and that at this stage I could not think of anything that his company could do to speed the process.

Mr. Barlow inquired as to whether I could personally intervene to expedite the review of this application, particularly given the critical nature of the application to his small company's success. I explained that we must be fair to all applicants and that we must review the applications according to workload and goal dates as established by PDUFA. Therefore, I declined to personally intervene with regard to this application beyond my usual level of direct involvement with an ongoing review and my stated goal to complete the review of applications as soon as possible and in advance of PDUFA goal dates whenever possible.

Mr. Barlow inquired as to how his company could receive updates on the progress of the review for purposes of corporate planning. I described the review process to him and explained that the project manager for the NDA is the appropriate person with whom his company could make periodic contact for updates on status of the NDA review. I specifically noted that hourly or daily calls for updates are disruptive and counterproductive to the conduct of the project manager's work and suggested that weekly or every other week might be a more appropriate schedule. I also explained to him why it was inefficient and counterproductive for reviewers to communicate deficiencies prior to completion of their review, although I noted that reviewers might communicate with the sponsor to request clarifications and/or additional data as needed during the course of a review. I reminded him that under FDAMA, once a review discipline completes their review that any deficiencies are forwarded to the sponsor promptly. I informed him that in the CMC arena we often are able to complete the review prior to the PDUFA goal date and are able to provide the sponsors with

deficiencies so that they can begin to address them as soon as possible. I did not provide him any estimate as to when any discipline's review would be completed other than my previous reference to completing our reviews and issuing an action letter before the PDUFA goal date.

Mr. Barlow seemed to understand the process that the Division follows with regard to the conduct of reviews and communicating with sponsors, however, he clearly remained concerned about the timeline for completion of the Xopenex review and approval of the product based on corporate considerations. I explained that I understood his concerns and pointed out that all sponsors who submit NDAs to us have similar concerns and that we receive frequent requests from sponsors that their applications receive a higher priority within the Division's review workload. I again informed him that we attempt to be fair to all sponsors and to meet the review goal dates outlined under PDUFA, but that we could not grant requests for higher priority status based on corporate concerns.

Mr. Barlow also inquired as to whether the interactions between the Division and his company had improved based on some recent personnel changes at Sepracor. I informed him that I could not provide any direct comment on that matter since I was not directly involved with day-to-day interactions with his staff. I suggested that the project managers in the Division would be most knowledgeable about this issue and suggested his contact Cathie Schumaker for an answer to his question.

The conversation was cordial throughout.

Follow-up action items:

1. Mr. Barlow to call Cathie Schumaker for feedback on interactions between Sepracor staff and the Division.

cc:
NDA 20-837
HFD-570/Division File
Jani
Jenkins

Jani

Minutes of Teleconference

NDA: 20-837 **Date:** October 21, 1998
Sponsor: Sepracor Inc.
Product: Levalbuterol Inhalation Solution
FDA Attendees: Jani, Jenkins
Sepracor Attendees: Mueller, Wachholz

Background: An approvable letter was sent to the sponsor on July 1, 1998. On August 6, 1998, Sepracor submitted a response to the AE letter, which they considered to be complete. This submission was reviewed by all the disciplines and it was determined that the response was incomplete, specifically item B.6 of the letter where the Agency had asked Sepracor to provide a [redacted] Only the safety breakdown in this patient population was provided in the August 6, 1998, submission. To facilitate the review process, a FAX was sent to Sepracor on August 28, 1998, which listed the deficiency and several other clarification points. Subsequently, a teleconference was held on September 9, 1998, to clarify the issues raised in the FAX. On September 24, 1998, Sepracor submitted their response to the FAX, which was considered complete and hence the UF clock was restarted. Sepracor was informed of the new UF goal date by a letter dated October 7, 1998.

Sepracor believed that the UF clock should have started based on their August 6, 1998, submission as they considered it a complete response to the AE letter. (See attached Sepracor Faxes dated October 16 and 19, 1998). The Division carefully reviewed these faxes, discussed the issues with Dr. Bilstad, and determined that as stated in out letter dated October 7, 1998, the UF due date for this application is March 25, 1999. This teleconference was held to clarify misunderstanding of the correct UF goal date.

The Division provided the following clarification to Sepracor.

- The July 1, 1998, approvable letter clearly stated that both safety and efficacy breakdown of the [redacted] should be submitted in the complete response. The August 6, 1998, contained only the safety breakdown, and hence the response was not considered complete. Item # 2 of the August 28, 1998 FAX clearly states that the efficacy breakdown was needed.

- The application is back on the review clock, and is in the queue for the review. The Division will meet the UF due date of March 25, 1999.

- The Division generally does not provide labeling comments until all the reviews are completed. As stated in our teleconference dated May 11, 1998, with Ms. Hall and Mr.

Barlow, Sepracor should not print any labeling until the NDA is approved. A product labeling is not final until the NDA is approved. Any label/labeling printed prior to the approval of the NDA will be at Sepracor's own risk.

- There are statements made by Sepracor to the trade press regarding the anticipated launch of this product. Sepracor should be aware that the Division at this point can not guarantee that the product will be approved in this cycle. The conclusion will be made upon completion of the review of the data submitted.

- Each review discipline works on multiple applications at a time and prioritizes his/her workload based on the due dates of each application. Sepracor should not assume that each discipline is currently actively reviewing their application. The Division will clearly meet the UF goal date.

Sepracor agreed that the August 6, 1998, submission did not contain the requested efficacy analysis in the [redacted] population and hence the response was not complete. Sepracor understood that labeling comments will be provided only after all the reviews are completed. The Division can not provide comments for carton/container labeling at this time, as the review of the scientific data is not completed.

/S/

Parinda Jani
Project Manager

APPEARS THIS WAY
ON ORIGINAL

MINUTES OF TELECONFERENCE

NDA: 20-837 **Date:** July 21, 1998
Sponsor: Sepracor Inc. **IMTS #** 3031
Product: **Xopenex** (levalbuterol hydrochloride) Inhalation Solution
Sepracor Attendees: Claus, DeGraw, Hall, Mueller, Reasner, Rubin, Tiso, Vaickus, Wachholz, Wald
FDA Attendees: Gillespie, Honig, Jani, Nicklas, Shah, Uppoor, Whitehurst

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Background: On July 1, 1998, an approvable letter was sent for NDA 20-837. Sepracor requested this telecon seeking clarification of the following issues.

1. **Confirm acceptance of all responses to DMF deficiencies letters**

   The Agency has received responses to the deficiencies letters by all the DMF holders. Whether the responses are adequate or not is a review issue. The responses will be reviewed upon receipt of the complete response to the AE letter. Since Sepracor has withdrawn the DMF for [redacted] in order for the Agency to review the response, Sepracor will have to provide proper Letter of Authorization (LOA) to reinstate this DMF.

2. **Adequacy of the 9- and 12-month stability data submitted May 28, 1998, to support the proposed storage conditions and expiration date**

   As stated in the approvable letter of July 1, 1998, the May 28, 1998, submission was acknowledged as correspondence and has not been reviewed by the Agency. The submission will be reviewed upon receipt of the complete response to the AE letter. Whether the data submitted will support the storage condition and the expiration dating period, is a review issue.

3. **Any additional questions raised from the review of the May 28, 1998, submission and whether the review is completed**

   See the response to item # 2.

4. **Any additional outstanding issues besides the one identified in the July 10, 1998, correspondence**

   In addition, Section A comment 12d regarding the [redacted] must be addressed adequately. Sepracor should also make sure that all the comments regarding the impurities are addressed adequately.

5. **Package labels**

Sepracor would like to know whether it is possible to finalize the immediate container labeling and the carton labeling within the next 2-3 weeks and whether the Agency could provide any preliminary comments for these labelings. Sepracor understands that printing/packaging any carton and container labels before the product is approved is their own risk.

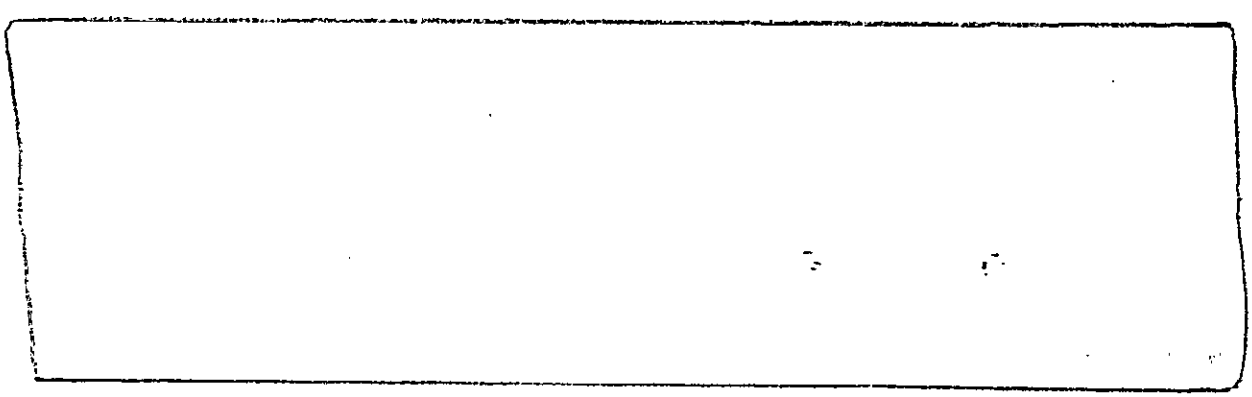
The Agency stated that the labeling is not finalized until all the reviews are completed. Sepracor should submit all the labeling with the complete response to the AE letter. (for the completion of the reviews, see response to item #2).

6. **Re-inspection of the facility**

The Division will initiate the request for reinspection when the complete response to the AE letter is received. The reinspection of the facility will have an impact on the approvability of the product.

7. **Format for the tables comparing "then and now" AEs (Item C.1)**

The Division's comment did not relate to tables for the package insert but to ease of review when the data are submitted.



9. **Accountability for subjects 004 and 014 (Item B.3)**

The results for these two subjects are unexpected/unanticipated which indicates that the lower dose for these patients may have been mislabeled. Sepracor should provide the data in a tabular form, stating what treatment these subjects received, and a footnote explaining the discrepancy.

10. **Exclusion of Dr. Edwards' data**

Dr. Edwards' site data should be excluded from the efficacy analysis of study 024. Conclusions regarding efficacy do not change if this site is excluded.

11. **Rationale for exclusion of 1.25 mg of racemic albuterol dose**

The 1.25 mg dose of racemic albuterol is not an approved dose for adults. Comparison of the response to different doses of racemic albuterol and levalbuterol in the labeling should therefore exclude reference to this dose. It was recommended that Sepracor rewrite this section in regard to excluding reference to the 1.25 mg dose of racemic albuterol and submit it with complete response to the AE letter.

12. **Rationale for exclusion of S-isomer references**

If Sepracor wants to include data referring to the S-isomer of albuterol in the labeling, it should not only be accurate but clearly clinically relevant.

13. **Blood-brain barrier statement**

This statement refers to the total albuterol measured in the racemic albuterol. The reference on which this statement is based, will be provided to Sepracor.

14. **Additional information describing secondary efficacy results**

If Sepracor wants to include information on secondary efficacy parameters in the labeling, this is acceptable, provided analysis of these parameters was part of the NDA submission and the Division has an opportunity to review any statements in the labeling related to these parameters.

15. **General meeting to finalize the labeling**

It is too premature to set the labeling meeting. A face-to-face meeting to finalize the labeling is usually not necessary, unless issues can not be resolved. In the future, if it becomes necessary to have a face-to-face meeting, the Agency will be happy to have such meeting..

Sepracor was informed of the review process when a complete response to the AE letter is submitted. The user fee clock will restart (date of receipt not the letter date of the submission) upon the Agency's determination that the response is complete. The review cycle is 6-months, i.e., the due date for the NDA will be 6-months from the date of the receipt of the complete response submission.

Parinda Jani
Project Manager

APPEARS THIS WAY ON ORIGINAL

Minutes of Teleconference

NDA: 20-837 **Date:** May 11, 1998
Sponsor: Sepracor Inc.
Product: Levalbuterol Inhalation Solution
FDA Attendees: Ms. Jani
Sepracor Attendees: Mr. Barlow, Ms. Hall

Background: The sponsor had originally proposed [redacted] as the tradename for this product. Because of several look alike/sound alike names, the LNC and the Division rejected the name. Subsequently, the sponsor proposed [redacted] or XOPENEX as the tradename. The name [redacted] was rejected for the same reasons as [redacted] however, XOPENEX will be acceptable as the tradename for this product.

The following information was conveyed to the sponsor.

1. The LNC and the Division have no objection to the name XOPENEX at this time. However, prior to the approval of the NDA, the LNC will be consulted again to ensure that no other products with a look alike/sound alike name has been approved by the Agency. This could make the name unacceptable.

2. Sepracor should not print any labeling until the NDA is approved. Any label/labeling that they print prior to the approval of the NDA will be at their own risk.

Note: On May 12, 1998, Miss Hall was informed that response to the IR letter that was sent on May 4, 1998, could trigger the extension of the review cycle. In that case, the due date will be October 1, 1998. Also, Ms. Hall was told that the labeling comments will not be sent until all the reviews are completed.

/S/

Parinda Jani
Project Manager

APPEARS THIS WAY
ON ORIGINAL

CC:
ORIG NDA 20-837
DIV FILE/HFD-570
HFD-570/JANI/5-11-98
HFD-570/NICKLAS, SHAH, WHITEHURST, ARAS, GILLESPIE
HFD-570/HONIG, POOCHIKIAN, SHEEVERS, WILSON, UPPOOR, JENKINSJ
HFD-570/SCHUMAKER

Jani

Minutes of Teleconference

NDA: 20-837
Sponsor: Sepracor Pharmaceuticals Inc.
Product: Levalbuterol Inhalation Solution

Date: January 6, 1998
IMTS # 2127

FDA Attendees:

Peter Honig, M.D.	Clinical Team leader
Parinda Jani	Project Manager
Richard Nicklas, M.D.	Clinical Reviewer
Vibhakar Shah, Ph.D.	Chemistry Reviewer

Sepracor Attendees:

David Barlow	President, Sepracor Pharmaceuticals Inc.
Pauliana Hall	Vice President, Worldwide Regulatory Affairs
John Simon	Group Product Manager, Respiratory
Joe West	Director, Marketing Planning and Research

Brand Institute Attendee:

James Dettore	President and CEO

Background: See submissions dated October 13 and December 8, 1997, and the facsimile transmission dated January 5, 1998.

On August 13, 1997, Sepracor was informed that the proposed name [redacted] was unacceptable due to look alike/sound alike names, specifically Zofran, Zosyn, and Zyban. In response, Sepracor submitted data from two market research studies in support of the name [redacted] The Division evaluated the data and concluded that the data did not discount or negate the concerns raised by the Agency. On November 26, 1997, Sepracor was informed of this decision. At Sepracor's request, this teleconference was scheduled to discuss Sepracor's position that the name was acceptable, based on market research studies.

Mr. Barlow discussed the objectives of the teleconference, and the naming process. In response to Dr. Nicklas' question, Sepracor indicated that they were pursuing the name [redacted] for various reasons including its uniqueness and memorability.

Dr. Nicklas stated that the Division continues to have the following concerns in regard to the name [redacted]

1. The Division continues to feel that there are too many look-alike/sound-alike names.

2. The type of marketing studies which Sepracor feels supports the name [redacted] are not validated. Although these marketing studies appear to support the use of the name [redacted], the methods used for conducting the studies are questionable (see comment below).

Mr. Dettore described the methodology used and how [redacted] has worked with several manufacturers to develop the methodology for these type of marketing studies.

As an example of the Division's concern about the conduct of the studies, Dr. Nicklas pointed out that it is not clear why patients and parents were chosen for the survey since they may not know all other drugs with similar names. If these individuals are removed from the survey, there is an approximately 30% mix-up in terms of products names.

Dr. Honig stated that since Sepracor is planning to [redacted] in future, it could magnify the name mix-up problems. In fact that the name begins with a letter "Z" is not a problem, but the spelling, the pronunciation, the number of syllables etc. all need to be considered when selecting a name. Consideration should be given to making the name more reflective of the product, but not a name that would incorporate the USAN and generic name.

Sepracor agreed to submit an alternate name. The Division will give the sponsor prompt feedback on whether it is acceptable.

[redacted] /S/

Parinda Jani
Project Manager

APPEARS THIS WAY
ON ORIGINAL

Memorandum of Telephone Facsimile Correspondence

Date: September 15, 1997

To: Pauliana Hall

From: Parinda Jani

Subject: NDA 20-837
Levalbuterol HCl
Telecon dated July 30, 1997

Reference is made to the telecon held between representatives of your company and this Division on July 30, 1997. Attached is a copy of our final minutes for that meeting. These minutes will serve as the official record of the telecon. If you have any questions or comments regarding the minutes, please call me at (301) 827-1064.

Thank you.

MINUTES OF TELECONFERENCE

NDA: 20-837 **DATE:** July 30, 1997

SPONSOR: Sepracor Inc.
PRODUCT: Levalbuterol HCL Inhalation Solution

FDA Attendees: Dr. Honig, Ms. Jani, Dr. Nicklas, Dr. Poochikian, Dr. Shah

SEPRACOR Attendees: Ms. Hall, Dr. Kellerman, Dr. Wald

BACKGROUND: The sponsor has not submitted any accelerated stability data for 40°C/10-20% RH/6-months for product wrapped within the foil-pouch, as requested by the Agency during the EOP 2 meeting.

Dr. Poochikian stated that the NDA as submitted will not support the room temperature [redacted] storage labeling. The length of time for the expiration will be determined after the review of the data is completed. To support the room temperature storage labeling, the Agency has always asked for stability data at 40°C/10-20% RH, 6-months for LDPE containers, to understand how the product will behave at high temperature. If problems are identified at 40°C/6-months, than it should be studied at 30°C for 12-months, but data are required to make the decision. This issue was discussed at the EOP 2 meeting. The Division recommended conducting stability study at 40°C/10-20% RH, for product wrapped within the foil-pouch, and provide minimum of 6-months data.

Sepracor responded that the degradation levels were very high at 40°C. Their interpretation of discussion at EOP 2 was that the recommendation was for out-of-pouch stability studies only. Sepracor was asked to submit one comprehensive package, that included a complete protocol (submitted July 1996).

The Division clarified that the purpose of asking for one comprehensive protocol was to conduct a complete review at one time, rather than responding to Sepracor's questions separately regarding issues related to the stability protocol. As submitted, the stability protocol may be adequate to support the refrigeration storage labeling. Whether the submitted data are adequate or not, is a review issue.

Dr. Poochikian said that the data submitted for 30°C/60%RH for 6-months, can be reviewed as long-term storage conditions to support the refrigeration storage labeling. For the room temperature storage labeling, it will depend on the time at which

6-months, 40°C/10-20% RH QA report data for product wrapped within the foil-pouch, is submitted during the review cycle. Alternatively, Sepracor can submit it as a "prior approval" supplement, after an action is taken (See the follow-up discussion below).

Also, Dr. Poochikian said that a complete impurity/degradation products profile (each individual impurity) in the drug substance, as well as in the drug product should be submitted. Appropriate specifications for each impurity/degradation products should be submitted based on the actual observed levels (not as [redacted]. Impurity/degradation products at 0.1% or greater level need to be monitored and specified. If these impurities happen to be solely of synthetic origin, it should be specified.

Sepracor will discuss the issue internally and will submit the stability protocol for comments from the Division. Sepracor understands that the NDA as submitted, will not support the room temperature storage labeling.

Follow-up discussion with Ms. Hall:

I explained to Ms. Hall how the review time is determined under PDUFA. The Agency has one year from the date of the receipt of an NDA to take an action. If a major amendment is submitted within the last 90 days of the due date, the review cycle can be extended for 90 days. The decision as to whether an amendment is major or not is made after the preliminary review of the submission. Once an action is taken, NA or AE, and the applicant submits a full response to all the deficiencies, the Agency has 6 months to complete the review and take an action.

/S/

Parinda Jani

project Manager