

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22442Orig1s000

OTHER REVIEW(S)

PMR: Pediatric Safety Study
Rezira: NDA 22-442

PMR/PMC Description: A study to assess the safety of Rezira (hydrocodone and pseudoephedrine combination product oral solution) in approximately 400-450 children 6-17 years of age with symptoms of the common cold. The study will be conducted with a formulation containing hydrocodone, chlorpheniramine, and pseudoephedrine. The dose used in this study will be based upon the results of the pharmacokinetic study in children ages 6 17 years.

PMR/PMC Schedule Milestones: Final Protocol Submission: 09/30/2014
Study/Trial Completion: 12/31/2015
Final Report Submission: 09/30/2016
Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre approval requirement. Check type below and describe.

- Unmet need
- Life threatening condition
- Long term data needed
- Only feasible to conduct post approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The product will be approved for the adult population. This PREA required PMR is for the Applicant to assess the safety of Zutripro and Rezira (hydrocodone, chlorpheniramine, and pseudoephedrine and hydrocodone and pseudoephedrine combination product oral solutions, respectively, in children 6 17 years of age. The dose(s) will be based on the results of a PK study which is also a PREA required PMR.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post approval, describe the "new safety information."

The Applicant's hydrocodone, chlorpheniramine, and pseudoephedrine and hydrocodone and pseudoephedrine cough and cold combination product oral solutions, Zutripro and Rezira, respectively, will be approved for adults 18 years of age and older based on previous FDA findings of efficacy and safety. However, the previous determinations of safety lacked sufficient data in children to accurately determine the proper dose and more fully assess the safety of the product, especially the hydrocodone (narcotic) component. Thus, pharmacokinetic and safety trials will be conducted as PREA requirements to help determine the dose and assess safety in children 6 17 years of age.

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3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A safety study of the Applicant's hydrocodone, chlorpheniramine, and pseudoephedrine combination product oral solution in approximately 400 children 6-17 years of age with cough and cold symptoms. This study will begin after analysis of the data collected from the pediatric pharmacokinetic study which will be conducted in order to assist in selecting the dose(s) of Zutripro and Rezira for the pediatric population ages 6-17 years.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

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Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

SALLY M SEYMOUR
06/07/2011

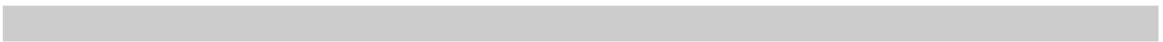
505(b)(2) ASSESSMENT

Application Information		
NDA # 22-442	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Rezira Established/Proper Name: hydrocodone and pseudoephedrine Dosage Form: oral solution Strengths: 5mg/60mg/ in 5 ml		
Applicant: Cypress Pharmaceutical, Inc.		
Date of Receipt: December 8, 2010		
PDUFA Goal Date: June 8, 2011	Action Goal Date (if different):	
Proposed Indication(s): Relief of cough and nasal congestion associated with common cold		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?
- YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA 05-213 Hycodan	Label Sections 1.0, 4.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 6.1, 7.1, 7.2, 8.1, 8.2, 8.3, 8.4, 8.6, 8.7, 8.8, 9.1, 9.2, 9.3, 10.1, 10.2, 12.1,
NDA 19-111 ** Tussionex Extended Release Suspension	Label Sections 5.4, 6.1, 8.5, 10.1, 12.1,
NDA 21-369 ** Codeprex Extended-Release Suspension	Label Section 7.3
21 CFR 201.57(c)(3) Specific requirements on content and format of labeling . . .	Label Section 8.1
21 CFR 341.72 Labeling of antihistamine drug products	Label Sections 1.0, 2.1, 2.2, 5.5, 17.1
21 CFR 341.80 Labeling of nasal decongestant drug products	Label Sections 1.0, 2.1, 2.2, 5.1, 5.6, 6.1, 7.2, 17.1
Mosby Drug Reference **	Label Sections 12.1

*each source of information should be listed on separate rows

**** Although the applicant cited reliance on this information in the cover letter and annotated labeling submitted in their original application, the review division has determined that reliance on this information is not necessary for approval.**

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

This application relies on a BA/BE study of the proposed product to the referenced products. No clinical studies for safety and efficacy were required to support this application.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO
If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO
If "NO," proceed to question #5.
If "YES", list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO
If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Hycodan	NDA 05-213	Y
Tussionex *	NDA 19-111	Y*
Tavist Allergy/Sinus *	NDA 21-082	Y *
Advil Allergy Sinus Caplets *	NDA 21-441	Y *

***Although the applicant cited reliance on this information in the cover letter and annotated labeling submitted in their original application, the review division has determined that reliance on this information is not necessary for approval**

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?
N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s)

Name of drug(s) approved in a 505(b)(2) application: **Tavist Allergy/Sinus**

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s)

Name of drug(s) approved via the DESI process: **Hycodan**

- c) Described in a monograph?

YES NO

If "YES", please list which drug(s)

Name of drug(s) described in a monograph:

Pseudoephedrine, 21 CFR §341.20

- d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing: **Hycodan**

- i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the

archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

- 9) Describe the change from the listed drug(s) relied upon to support 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 capsule to solution”).

This application provide for a new combination drug product.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

- 10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(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)).*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

*If “NO” to (a) proceed to question #11.
If “YES” to (a), answer (b) and (c) then proceed to question #12.*

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

- (c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES NO

If “YES” to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If “NO” or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(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.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO
If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES NO

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed proceed to question #14

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) 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.)*

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

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

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):

Expiry date(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). *If Paragraph IV certification was submitted, proceed to question #15.*

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

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):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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/s/

PHILANTHA M BOWEN
06/02/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Date: June 2, 2011

Reviewers: Richard Abate, RPh, MS, Safety Evaluator
and
Anne Tobenkin, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Through: Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

Subject: Labeling and Packaging Review

Drug Names and Strengths: Zutripro (Hydrocodone Bitartrate, Chlorpheniramine Maleate, and Pseudoephedrine Hydrochloride) Oral Solution, 5 mg/4 mg/60 mg per 5 mL

Rezira (Hydrocodone Bitartrate and Pseudoephedrine Hydrochloride) Oral Solution, 5 mg/60 mg per 5 mL

Application Type/Numbers: NDA 022439 (Zutripro)
NDA 022442 (Rezira)

Applicant/sponsor: Cypress
Pharmaceuticals

OSE RCM #: 2011-328-1 and 2011-379-1

1 INTRODUCTION

This review evaluates the revised fill volume of the professional samples from (b) (4) to 5 mL for Zutripro (Hydrocodone Bitartrate, Chlorpheniramine Maleate, and Pseudoephedrine Hydrochloride) Oral Solution for NDA 022439 and Rezira Hydrocodone Bitartrate and Pseudoephedrine Hydrochloride) Oral Solution for NDA 022442. This Applicant submitted the revision pursuant to a request from the Division of Pulmonary, Allergy and Rheumatology Products on May 25, 2011 following DMEPA's recommendation not to approve the (b) (4) size for safety reasons (see OSE reviews #2011-328 dated May 2, 2011 and OSE review # 2011-37 dated May 24, 2011 for Rezira Hydrocodone Bitartrate and Pseudoephedrine Hydrochloride) Oral Solution.)

2 DISCUSSION AND CONCLUSIONS

Following receipt of DMEPA's recommendations, the Applicant submitted revised container labels and carton labeling for both Zutripro (NDA 022439) and Rezira (NDA 022442) with revised fill volumes for the professional samples of each product to 5 mL or one dose. Therefore, DMEPA agrees with the approval of the professional samples with a 5 mL fill volume as presented in the May 27, 2011 submissions for Zutripro (NDA 022439) and Rezira (NDA 022442). Additionally, DMEPA communicated the acceptability of the revised container labels and carton labeling via e-mail to DPARP on Tuesday, May 31, 2011.

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/s/

RICHARD A ABATE
06/02/2011

CAROL A HOLQUIST
06/02/2011

MEMORANDUM

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

TO: NDA 022439
NDA 022442

FROM: Kim Quaintance
Associate Director for Regulatory Affairs
Office of New Drugs

SUBJECT: Addendum to 505(b)(2) Assessments

This memorandum seeks to further clarify the listed drug relied upon to support approval of the proposed 505(b)(2) applications.

The applicant for NDA 022439 and NDA 022442, Cypress Pharmaceuticals, Inc., (Cypress) cited reliance on FDA's finding of safety and effectiveness for Hycodan Syrup (NDA 005213, applicant: Endo Pharmaceuticals), Tussionex Extended Release Suspension (NDA 019111, applicant: UCB Inc), and Codeprex Extended Release Suspension (NDA 021369, applicant: UCB Inc) to support approval of its 505(b)(2) application in their original application received November 7, 2008 and November 10, 2008, respectively. In the applicant's responses to our Complete Response letters, Cypress added another listed drug relied upon to support approval of its 505(b)(2) applications: Hi-Tech Syrup (ANDA 040613, applicant: Hi Tech Pharmacal Co, Inc.) but did not indicate that it no longer sought to rely on Hycodan Syrup.

Hycodan Syrup is listed in the "Discontinued" section of the Orange Book, but was not withdrawn from sale for reasons of safety or effectiveness. Cypress conducted bioequivalence trials with Hycodan Syrup before it was discontinued.

As outlined in the (b)(2) assessments, while the applicant cited reliance on Tussionex and Codeprex, the review division determined that reliance on these two listed drugs was not necessary for approval of these (b)(2) applications.

Although it was approved in an ANDA, Hi-Tech Syrup is designated in the Orange Book as a reference listed drug (RLD) because Hycodan Syrup, the previous RLD, has been discontinued. Given that only a listed drug approved for safety and effectiveness under section 505(c) of the FFD&C Act (as distinguished from a drug approved in an ANDA under section 505(j) of the FFD&C Act) may be relied upon to support approval of a 505(b)(2) application, this 505(b)(2) application cannot rely upon Hi-Tech Syrup to support its approval.

Therefore, this 505(b)(2) application solely relies upon FDA's finding of safety and effectiveness for Hycodan Syrup (NDA 005213).

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22439	ORIG-1	CYPRESS PHARMACEUTICA L INC	(b) (4) HYDROCODONE BITARTRATE/CHLORPH
NDA-22442	ORIG-1	CYPRESS PHARMACEUTICA L INC	REZIRA (b) (4) (HYDROCODONE BITARTRATE AND PSEU

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/s/

KIM M Quaintance
05/27/2010

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medication Error Prevention and Risk Management**

Label and Labeling Review

Date: May 24, 2011

Reviewer(s): Anne C. Tobenkin, Pharm.D., Safety Evaluator
Division of Medication Error Prevention and Analysis

Team Leader Melina Griffis, RPh, Team Leader
Division of Medication Error Prevention and Analysis

Division Director Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Rezira (Hydrocodone Bitartrate and Pseudoephedrine
Hydrochloride) Oral Solution, 5 mg/60 mg per 5 mL

Application Type/Number: NDA 022442

Applicant/sponsor: Cypress Pharmaceuticals

OSE RCM #: 2011-379

1 INTRODUCTION

This review summarizes the Division of Medication Error Prevention and Analysis (DMEPA) evaluation of the proposed container labels, carton and insert labeling for Rezira (Hydrocodone Bitartrate and Pseudoephedrine HCl) Oral Solution. DMEPA evaluates the labels and labeling for vulnerabilities and confusion that may lead to medication errors.

1.1 REGULATORY HISTORY

DMEPA previously reviewed container labels and carton and insert labeling in OSE review # 2009-2442 dated May 7, 2010. Our comments were forwarded to the Applicant, but the NDA received a Complete Response June 11, 2010.

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis¹ and human factor principles, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted December 8, 2010
- Carton Labeling submitted December 8, 2010
- Insert Labeling submitted December 8, 2010

3 DISCUSSION OF DEFICIENCIES IDENTIFIED

DMEPA identified the following deficiencies related to Rezira.

3.1 PRODUCT DESIGN

The professional samples are packaged as (b) (4). Thus, we believe the net quantity of Rezira in the professional sample is likely to be mistaken for a single dose and administered at one time resulting in an overdose.

3.2 CONTAINER LABELS, CARTON LABELING AND INSERT LABELING

We note the proposed labels and labeling include the previously requested revisions per OSE review # 2009-2442. However, DMEPA noted additional findings which may lead to confusion with the sample container and sample carton labeling. We provide comments to the Applicant in section 5 below.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA identified vulnerabilities with the labels and labeling which may result in confusion resulting in a medication error. In addition, the fill volume of the professional sample introduces vulnerability that can lead to medication errors because the entire volume (b) (4) is a commonly used volume for adult doses of oral liquids and thus may

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

result in an overdose if administered in its entirety. DMEPA recommends the Rezira professional samples be revised prior to approval. Please forward the comments in section 5 to the Applicant.

5 COMMENTS TO THE APPLICANT

A. General Comment

Limit the fill volume of the Rezira professional sample presentation to a 5 mL to minimize the risk of accidental overdose with this product.

B. Carton Labeling

1. Revise the Professional Sample statement on the carton labeling to read, 'Professional Samples' so that it appropriately reflect that the carton contains multiple samples.
2. Include the contents statement (e.g. 12 bottles) on the carton flap to ensure that the contents of the carton are visible.

C. Container Label

The 'Professional Sample' statement which is oriented vertically on the side of this label and should be oriented horizontally and relocated to the principle display panel to increase its readability.

If you have further questions or need clarifications, please contact Nichelle Rashid, project manager, at 301-796-3904.

1 page of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

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/s/

MELINA N GRIFFIS
05/24/2011

CAROL A HOLQUIST
05/25/2011

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

*****Pre-decisional Agency Information*****

Memorandum

Date: May 4, 2011

To: Philantha Bowen, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
(DPARP)

From: Roberta Szydlo, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications
(DDMAC)

CC: Lisa Hubbard, Professional Group Leader
Robyn Tyler, Acting DTC Group Leader
Matthew Falter, Regulatory Review Officer
Olga Salis, Regulatory Health Project Manager
Michael Wade, Regulatory Health Project Manager
(DDMAC)

Subject: NDA # 022442
DDMAC labeling comments for REZIRA (hydrocodone bitartrate,
and pseudoephedrine hydrochloride) Oral Solution (Rezira)

DDMAC has reviewed the revised proposed prescribing information (PI) and the proposed carton/container labeling for Rezira submitted for consult on January 25, 2011.

DDMAC's comments on the PI are based on the proposed draft marked-up labeling titled "NDA 22442 – FDA Proposed Label (4-27-11).doc" that was sent via email from DPARP to DDMAC on April 27, 2011. DDMAC's comments on the PI are provided directly in the marked-up document attached (see below).

DDMAC has reviewed the proposed carton/container labeling located in the EDR at: <\\cdsesub1\EVSPROD\NDA022442\0016\m1\us\114-labeling\1141-draft-labeling\11411-draft-carton-container-labels\draft-carton-container-labels.pdf>. We have no comments at this time on the proposed carton/container labeling.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions, please contact Roberta Szydlo at (301) 796-5389 or roberta.szydlo@fda.hhs.gov.

15 pages of draft labeling have been withheld in full as B(4) CCI/TS immediately following this page

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/s/

ROBERTA T SZYDLO
05/04/2011

REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

Application: NDA 22442/000
Name of Drug: REZIRA (hydrocodone and pseudoephedrine)

Applicant: Cypress Pharmaceuticals
Review Date: May 3, 2011

Labeling Reviewed

Submission Date: December 8, 2010

Receipt Date: December 8, 2010

Background and Summary Description

On December 8, 2010, Cypress Pharmaceuticals resubmitted a 505(b)(2) New Drug Application for hydrocodone and pseudoephedrine for the relief of cough and nasal congestion associated with common cold.

The proposed labeling was provided in SPL, including electronic carton and container labels.

OSE and DDMAC will be consulted regarding the labeling, as appropriate to their discipline, for recommendations regarding the proposed content.

Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" section of this review. Labeling deficiencies are identified in this section with an "X" in the checkbox next to the labeling requirement.

- Replace "TRADENAME" with the accepted name "REZIRA" in the Highlight Section - *Drug Interaction Section* of the package insert.
- Change Initial U.S. Approval date to 2011

Conclusions/Recommendations

All labeling deficiencies identified in the SRPI section of this review will be conveyed to the applicant in the Division's initial request for labeling revisions. The applicant will be asked to resubmit labeling that addresses all identified labeling deficiencies. The resubmitted labeling will be used for further labeling discussions.

Selected Requirements for Prescribing Information (SRPI)

Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• Highlights Limitation Statement (required statement)
• Drug names, dosage form, route of administration, and controlled substance symbol, if applicable (required information)
• Initial U.S. Approval (required information)
• Boxed Warning (if applicable)
• Recent Major Changes (for a supplement)
• Indications and Usage (required information)
• Dosage and Administration (required information)
• Dosage Forms and Strengths (required information)
• Contraindications (required heading if no contraindications are known, it must state "None")
• Warnings and Precautions (required information)
• Adverse Reactions (required AR contact reporting statement)
• Drug Interactions (optional heading)
• Use in Specific Populations (optional heading)
• Patient Counseling Information Statement (required statement)
• Revision Date (required information)

- **Highlights Limitation Statement**

- Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

- **Product Title**

- Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**

- The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**

- All text in the boxed warning is **bolded**.
- Summary of the warning must not exceed a length of 20 lines.
- Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
- Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**

- Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
- The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
- For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
- A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
- Removal of a section or subsection should be noted. For example, “Dosage and

Administration, Coronary Stenting (2.2) --- removal 2/2010.”

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)].” Identify the established pharmacologic class for the drug at:
<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**”.

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI)

• General Format

- A horizontal line must separate the TOC and FPI.
- The heading **FULL PRESCRIBING INFORMATION** must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

• Boxed Warning

- Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

• Contraindications

- For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.
- For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”
- For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- This section is required and cannot be omitted.
- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:
 - “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

See Appended Electronic Signature

Regulatory Project Manager

Date

Chief, Project Management Staff

Date

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/s/

PHILANTHA M BOWEN
05/05/2011

SANDRA L BARNES
05/05/2011

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Pulmonary and Allergy Products

Application Number: NDA 22-442/S-000

Name of Drug: Rezira (hydrocodone and pseudoephedrine) oral solution

Applicant: Cypress Pharmaceuticals

Material Reviewed:

Submission Date(s): December 10, 2009 and May 17, 2010

Receipt Date(s): December 11, 2009 and May 17, 2010

Submission Date of Structure Product Labeling (SPL): December 10, 2009

Type of Labeling Reviewed: Package Insert, Carton, and Container

Background and Summary

On December 10, 2009, Cypress Pharmaceuticals resubmitted a New Drug Application for Rezira for (b) (4) relief of cough and nasal congestion associated with common cold.

The proposed labeling text for Rezira was provided in SPL and draft labeling text, including carton and container labels.

OSE and DDMAC were consulted regarding the proposed labeling for recommendations regarding the content.

Review

The proposed labeling was reviewed using the Label Review Tool provided by SEALD. I identified the following comments pertaining to the format of the Full Prescribing Information-Table of Contents and Details sections of the product label:

The Division sent a facsimile dated May 5, 2010, to Cypress containing a marked-up version of the PI illustrating recommended labeling revisions, including the consult recommendations and the format comments listed above. Also on May 12, 2010, additional labeling comments were sent to Cypress via facsimile.

Cypress submitted a response dated May 17, 2010. The amendment contained draft labeling text for the package insert and carton and container labels. All changes were made to the proposed package insert and carton and container labels as recommended in the facsimiles with the exception of the request to move the contents statement to the side panel on the 16 fl oz bottle label. Cypress explained that the right panel on the label proof appears to be blank and available for text; however, it is actually a clear panel that shows the first page of the package insert under the clear panel. The format informs the pharmacist that the package insert is available under the wrapping bottle label. Cypress has adjusted the principal display panel to maximize the separation and clarity of the text.

Recommendations

The recommended action for this application is a complete response based on the deficiencies identified in the Division of Scientific Investigations bioequivalence establishment inspection reports dated May 5 and 25, 2010.

Carol Hill for
Philantha M. Bowen
Regulatory Project Manager
CDER, OND, ODE II

Supervisory Comment/Concurrence:

Sandy Barnes
Chief, Project Management Staff
CDER, OND, ODE II

Drafted: Bowen/February 24, 2010

Hill/June 4, 2010

Initialed: Barnes/June 9, 2010

Finalized: Hill for Bowen/June 10, 2010

Filename: N22-442 (000) Resub I PLR Review

CSO LABELING REVIEW OF PLR FORMAT

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22442	ORIG-1	CYPRESS PHARMACEUTICA L INC	REZIRA (hydrocodone bitartrate and PSEU)

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/s/

CAROL F HILL
06/11/2010

SANDRA L BARNES
06/18/2010

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

*****Pre-decisional Agency Information*****

Memorandum

Date: May 10, 2010

To: Carol Hill, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
(DPARP)

From: Roberta Szydlo, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications
(DDMAC)

Through: Lisa Hubbard, Professional Group Leader

CC: Sangeeta Vaswani, DTC Group Leader
Robyn Tyler, Regulatory Review Officer
Wayne Amchin, Regulatory Health Project Manager
(DDMAC)

Subject: NDA # 022442
DDMAC labeling comments for REZIRA™ (hydrocodone bitartrate
and pseudoephedrine hydrochloride) Oral Solution

DDMAC has reviewed the revised proposed product labeling (PI) for REZIRA™ (hydrocodone bitartrate and pseudoephedrine hydrochloride) Oral Solution submitted for consult on December 23, 2009. DDMAC's comments are based on the proposed draft marked-up labeling titled "N22442 REZIRA Oral Solution FDA labeling edits May 5.doc" that was sent via email from DPARP to DDMAC on May 5, 2010.

DDMAC's comments on the PI are provided directly in the marked-up document attached (see below).

Thank you for the opportunity to comment on these proposed materials.

If you have any questions regarding the PI, please contact Roberta Szydlo at (301) 796-5389 or roberta.szydlo@fda.hhs.gov.

16 pages of draft labeling have been withheld in full as B(4) CCI/TS immediately following this page

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22442

ORIG-1

CYPRESS
PHARMACEUTICA
L INC

REZIRA^(b)₍₄₎ (HYDROCODONE
BITARTRATE AND PSEU

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/s/

ROBERTA T SZYDLO

05/10/2010



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: May 7, 2010

To: Badrul Chowdhury, MD, Director
Division of Pulmonary, Allergy and Rheumatology Products

Through: Zachary Oleszczuk, PharmD, Acting Team Leader
Denise Toyer, PharmD, Deputy Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Felicia Duffy, RN, BSN, MSED, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name: Rezira (Hydrocodone Bitartrate and Pseudoephedrine HCl) Oral
Solution
5 mg/60 mg per 5 mL

Application Type/Number: NDA 022442

Applicant: Cypress Pharmaceuticals

OSE RCM #: 2009-2442

1 INTRODUCTION

This review is written in response to a request from the Division of Pulmonary, Allergy, and Rheumatology Products for the assessment of labels and labeling for Rezira (Hydrocodone bitartrate and Pseudoephedrine HCl) Oral Solution for their vulnerability to medication errors.

2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis¹ (FMEA) in our evaluation of the container label, carton labeling and insert labeling that were submitted by the Applicant on November 7, 2008 and resubmitted on December 10, 2009 (see Appendices A and B; no image of insert labeling).

3 RECOMMENDATIONS

Our evaluation noted areas where information on the label and labeling can be clarified and improved upon to minimize the potential for medication errors. Section 3.1 (*Comments to the Division*) contains our recommendations for the insert labeling. Section 3.2 (*Comments to the Applicant*) contains our recommendations for the container label and carton labeling. We request these recommendations be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Carolyn Volpe, OSE Regulatory Project manager, at 301-796-5204.

3.1 COMMENTS TO THE DIVISION

We note that the dose is presented in both (b) (4) and milliliters throughout the insert labeling (b) (4). Since the insert is geared towards healthcare providers, we recommend presenting the dose only in the metric units (i.e., mL) in order to avoid dosing errors or confusion between (b) (4) and milliliters.

3.2 COMMENTS TO THE APPLICANT

A. Container Label (b) (4) 480 mL)

1. As currently presented, the similar color scheme between Rezira and (b) (4) container labels may increase the potential for shelf selection errors if the products are stored by established name. Therefore, in order to minimize the potential for selection errors, use a different color scheme for Rezira and (b) (4) (b) (4)

2. The thin font used for the established name and product strength is difficult to read because the letters appear compacted. Revise the font of the established name and product strength in order to improve readability.

¹ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

3. As currently presented, the product strength (5 mg/60 mg per 5 mL) is not prominent and is difficult to find. Increase the prominence of the product strength by highlighting, boxing, color, or some other means. Additionally, add white space between the established name and product strength in order to increase the prominence of the product strength.
4. The principle display panel of the 480 mL container label appears cluttered. Relocate the contents statement to the side panel to provide more room to increase the prominence of the product strength.
5. The contents statement is confusing as it contains information for the contents per (b) (4) and per 5 mL (see below).

(b) (4) (b) (4)
Contains:
 Hydrocodone
 Bitartrate (b) (4) 5 mg
WARNING: May be habit forming.
 Pseudoephedrine
 Hydrochloride ... (b) (4) 60 mg

Since practitioners can calculate the amount per (b) (4) and in order to avoid confusion, we recommend deleting the (b) (4) column since the concentration of the product is per 5 mL. Revise the Per 5 mL column to delete (b) (4) and revise the statement of strength as follows:

Contains:
 Hydrocodone
 Bitartrate.....5 mg/5 mL
Warning: May be habit forming.
 Pseudoephedrine HCl.....60 mg/5 mL

6. Delete following statement on the side panel of the 480 mL container label: (b) (4) as this drug does not contain patient package insert labeling.

B. Carton Labeling (b) (4) **12 count)**

1. See Comments A3 and A5.
2. The thin white font on the red background containing the established name, product strength, usual dosage information, and warning information is difficult to read. Revise the prominence of the font in order to increase its readability.

2 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22442	ORIG-1	CYPRESS PHARMACEUTICA L INC	REZIRA ^(b) ₍₄₎ (HYDROCODONE BITARTRATE AND PSEU

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/s/

FELICIA DUFFY
05/07/2010

ZACHARY A OLESZCZUK
05/07/2010

DENISE P TOYER
05/07/2010

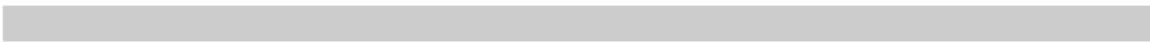
505(b)(2) ASSESSMENT

Application Information		
NDA # 22-442	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Rezira Established/Proper Name: hydrocodone and pseudoephedrine Dosage Form: oral solution Strengths: 5mg/60mg/ in 5 ml		
Applicant: Cypress Pharmaceutical, Inc.		
Date of Receipt: December 11, 2010		
PDUFA Goal Date: June 11, 2010		Action Goal Date (if different):
Proposed Indication(s): Relief of cough and nasal congestion associated with common cold		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?
- YES NO

If "YES "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA 05-213 Hycodan	Label Sections 1.0, 4.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 6.1, 7.1, 7.2, 8.1, 8.2, 8.3, 8.4, 8.6, 8.7, 8.8, 9.1, 9.2, 9.3, 10.1, 10.2, 12.1,
NDA 19-111 ** Tussionex Extended Release Suspension	Label Sections 5.4, 6.1, 8.5, 10.1, 12.1,
NDA 21-369 ** Codeprex Extended-Release Suspension	Label Section 7.3
21 CFR 201.57(c)(3) Specific requirements on content and format of labeling . . .	Label Section 8.1
21 CFR 341.72 Labeling of antihistamine drug products	Label Sections 1.0, 2.1, 2.2, 5.5, 17.1
21 CFR 341.80 Labeling of nasal decongestant drug products	Label Sections 1.0, 2.1, 2.2, 5.1, 5.6, 6.1, 7.2, 17.1
Mosby Drug Reference **	Label Sections 12.1

*each source of information should be listed on separate rows

** Although the applicant cited reliance on this information in the cover letter and annotated labeling submitted in their original application, the review division has determined that reliance on this information is not necessary for approval.

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

This application relies on a BA/BE study of the proposed product to the referenced products. No clinical studies for safety and efficacy were required to support this application.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO
If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO
If "NO", proceed to question #5.
If "YES", list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO
If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Hycodan	NDA 05-213	Y
Tussionex *	NDA 19-111	Y*
Tavist Allergy/Sinus *	NDA 21-082	Y *
Advil Allergy Sinus Caplets *	NDA 21-441	Y *

*Although the applicant cited reliance on this information in the cover letter and annotated labeling submitted in their original application, the review division has determined that reliance on this information is not necessary for approval

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?
N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s)

Name of drug(s) approved in a 505(b)(2) application: **Tavist Allergy/Sinus**

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process: **Hycodan**

- c) Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

Pseudoephedrine, 21 CFR §341.20

- d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing: **Hycodan**

- i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

- 9) Describe the change from the listed drug(s) relied upon to support 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 capsule to solution”).

This application provides for a new combination drug product.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

- 10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(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)).*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

*If “NO” to (a) proceed to question #11.
If “YES” to (a), answer (b) and (c) then proceed to question #12.*

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

- (c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES NO

If “YES” to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If “NO” or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(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.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES NO

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

14) 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.*)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 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):

Expiry date(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). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 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):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?
YES NO
If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.
YES NO
If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22442

ORIG-1

CYPRESS
PHARMACEUTICA
L INC

REZIRA^(b)₍₄₎ (HYDROCODONE
BITARTRATE AND PSEU

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/s/

CAROL F HILL
05/27/2010

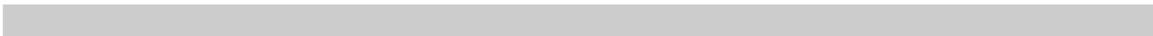
505(b)(2) ASSESSMENT

Application Information		
NDA # 22-442	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Rezira Established/Proper Name: hydrocodone and pseudoephedrine Dosage Form: oral solution Strengths: 5mg/60mg/ in 5 ml		
Applicant: Cypress Pharmaceutical, Inc.		
Date of Receipt: November 10, 2008		
PDUFA Goal Date: September 10, 2009		Action Goal Date (if different): September 17, 2009
Proposed Indication(s): (b) (4) relief of cough and for the (b) (4) relief of nasal congestion due to the common cold		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?
- YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA 05-213 Hycodan	Label Sections 1.0, 4.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 6.1, 7.1, 7.2, 8.1, 8.2, 8.3, 8.4, 8.6, 8.7, 8.8, 9.1, 9.2, 9.3, 10.1, 10.2, 12.1,
NDA 19-111 ** Tussionex Extended Release Suspension	Label Sections 5.4, 6.1, 8.5, 10.1, 12.1,
NDA 21-369 ** Codeprex Extended-Release Suspension	Label Section 7.3
21 CFR 201.57(c)(3) Specific requirements on content and format of labeling . . .	Label Section 8.1
21 CFR 341.72 Labeling of antihistamine drug products	Label Sections 1.0, 2.1, 2.2, 5.5, 17.1
21 CFR 341.80 Labeling of nasal decongestant drug products	Label Sections 1.0, 2.1, 2.2, 5.1, 5.6, 6.1, 7.2, 17.1
Mosby Drug Reference **	Label Sections 12.1

*each source of information should be listed on separate rows

** Although the applicant cited reliance on this information in the cover letter and annotated labeling submitted in their original application, the review division has determined that reliance on this information is not necessary for approval.

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

This application relies on a BA/BE study of the proposed product to the referenced products. No clinical studies for safety and efficacy were required to support this application.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO
If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO
If "NO," proceed to question #5.
If "YES", list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO
If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Hycodan	NDA 05-213	Y
Tussionex *	NDA 19-111	Y*
Tavist Allergy/Sinus *	NDA 21-082	Y *
Advil Allergy Sinus Caplets *	NDA 21-441	Y *

*Although the applicant cited reliance on this information in the cover letter and annotated labeling submitted in their original application, the review division has determined that reliance on this information is not necessary for approval

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?
N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s)

Name of drug(s) approved in a 505(b)(2) application: **Tavist Allergy/Sinus**

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process: **Hycodan**

- c) Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

Pseudoephedrine, 21 CFR §341.20

- d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing: **Hycodan**

- i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

- 9) Describe the change from the listed drug(s) relied upon to support 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 capsule to solution”).

This application provide for a new combination drug product.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

- 10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(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)).*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

*If “NO” to (a) proceed to question #11.
If “YES” to (a), answer (b) and (c) then proceed to question #12.*

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

- (c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES NO

*If “YES” to (c) **and** there are no additional pharmaceutical equivalents listed, proceed to question #12.*

*If “NO” **or** if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do **not** have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(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.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES NO

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

14) 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.*)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 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):

Expiry date(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). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 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):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?
YES NO
If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.
YES NO
If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22442

ORIG-1

CYPRESS
PHARMACEUTICA
L INC

REZIRA-^(b)₍₄₎ (HYDROCODONE
BITARTRATE AND PSEU

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/s/

PHILANTHA M BOWEN

09/17/2009

MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 11, 2009

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

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff (CSS)

From: Lori A. Love, M.D. Ph.D., Lead Medical Officer, CSS

Subject: CSS Recommendations:
* NDA 22-439 - (b) (4) (hydrocodone, chlorpheniramine, &
pseudoephedrine) Oral Solution
* NDA 22-442 - REZIRA (b) (4) (hydrocodone & pseudoephedrine) Oral
Solution,

Materials reviewed: Materials submitted and comprising the NDAs that CSS was consulted on. Minutes of the Regulatory Briefing on Abuse Potential Safety Testing for Hydrocodone Cough and Cold Combination Products held June 12, 2009. The OSE Review of August 26, 2009.

The Controlled Substance Staff (CSS) was consulted on NDAs for hydrocodone combination products currently under review in the Division of Pulmonary and Allergy Products (DPAP). CSS was asked to assess these products for abuse potential and for scheduling status under the Controlled Substances Act (CSA). Dr. James Tolliver (Pharmacologist, CSS) responded by memo of September 3, 2009 (NDA 22-439 and NDA 22-442). In a subsequent discussion between CSS and DPAP, CSS determined that further clarification of the recommendations was appropriate.

The recommendations below are also relevant to the following submissions:

(b) (4)
(b) (4)
(b) (4)

Recommendation

CSS recommends that each Sponsor conduct active surveillance and monitoring of their respective drug products for signals of abuse, misuse, overdose and addiction. The Sponsor should provide periodic analysis and summary of surveillance and monitoring

activities for abuse, misuse, overdose, and addiction for a period of five years. The Sponsor should provide periodic assessments for the first 6 months post approval and then annually unless a signal is identified. Outcomes and any interventions that were taken should be described.

Discussion

Drug abuse data bases show that hydrocodone is one of the most abused opioid drugs in the United States. In addition, medical examiner reports show that hydrocodone is associated with many deaths. Over the past several years on numerous occasions, FDA/CDER has been requested to respond to regulatory issues dealing with the abuse, misuse, addiction, and overdose of hydrocodone. In order to differentiate the abuse potential of distinct hydrocodone products, CSS proposed that animal and human abuse liability laboratory pharmacology studies be conducted pre-approval. The regulatory briefing panel did not see the need for any laboratory abuse studies for the individual products, unless the individual product had demonstrated a signal for abuse. At present, there is a problem with generation of such a signal for any of the individual products. The Office of Surveillance and Epidemiology (OSE) consult discussed the signal limitations in its review. Applying the evidence found in the Drug Abuse Warning Network (DAWN), OSE advised that the abuse of the hydrocodone cough-cold products appears to be lower than for analgesic hydrocodone products. However, because of the data limitations, OSE recommended that further abuse liability assessment be conducted post-approval on all hydrocodone containing cough cold products submitted as NDAs.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22442	ORIG-1	CYPRESS PHARMACEUTICA L INC	REZIRA- ^(b) ₍₄₎ (HYDROCODONE BITARTRATE AND PSEU

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

/s/

LORI A LOVE
09/11/2009

MICHAEL KLEIN
09/11/2009



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 3, 2009

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

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff (CSS)

Lori A. Love, M.D. Ph.D., Lead Medical Officer, CSS

From: James M. Tolliver, Ph.D., Pharmacologist, CSS
Controlled Substance Staff (CSS)

Subject: Consult on NDAs 22-439 for (b) (4) (hydrocodone, chlorpheniramine, and pseudoephedrine) Oral Solution and 22-442 for REZIRA™ (b) (4) (hydrocodone and pseudoephedrine) Oral Solution Sponsor: Cypress Pharmaceuticals, Inc..

Materials reviewed: All materials submitted and comprising NDA 22-439 and NDA 22-442. Minutes of the Regulatory Briefing on Abuse Potential Safety Testing for Hydrocodone Cough and Cold Combination Products held June 12, 2009 and the OSE Review of August 26, 2009.

Background:

Cypress Pharmaceuticals, Inc. (Sponsor) submitted for approval to the FDA NDA 22-439 for (b) (4) Oral Solution and NDA 22-442 for REZIRA™ (b) (4) Oral Solution. The Sponsor is using the 505(b)(2) regulatory pathway with reliance on DESI Notice #5213 (37 F.R. 7827), reference products Hycodan (NDA 5-213) and Tussionex Extended-Release Suspension (NDA 19-111), medical literature and the OTC Monographs for chlorpheniramine maleate and pseudoephedrine HCl. On January 14, 2008, the Sponsor met with the FDA to discuss requirements for six hydrocodone products under development, including (b) (4) Oral Solution and REZIRA™ (b) (4) Oral Solution. Based upon an examination of the minutes of this meeting dated February 6, 2008, there was no discussion of the abuse potential or scheduling for these products. At the request of the Division of Pulmonary & Allergy Products, CSS reviewed both NDAs for abuse potential and recommendation for drug scheduling.

(b) (4) Oral Solution is formulated such that each (b) (4) (5 mL) contains: hydrocodone bitartrate, 5 mg; chlorpheniramine maleate, 4 mg; and pseudoephedrine

hydrochloride, 60 mg. The product is indicated for the (b) (4) relief of cough; (b) (4) or other upper respiratory allergies (b) (4) and the (b) (4) relief of nasal congestion due to the common cold. For adults (b) (4) the dosage regimen is one (b) (4) (5 mL) every 4 to 6 hours as (b) (4) needed, not to exceed 4 doses (20 mL) in 24 hours. (b) (4)

Each (b) (4) (5 mL) of REZIRA™ (b) (4) Oral Solution contains hydrocodone bitartrate, 5 mg; and pseudoephedrine hydrochloride, 60 mg. The product is indicated for the (b) (4) relief of cough and (b) (4) relief of nasal congestion due to the common cold. For adults (b) (4) the dosage regimen is (b) (4) (5 mL) every 4 to 6 hours as needed, not to exceed 4 doses (20 mL) in 24 hours. (b) (4)

Currently, all marketed hydrocodone products are formulated as hydrocodone in combination with a nonnarcotic drug present in a recognized therapeutic amount, and are in Schedule III of the Controlled Substances Act. These drug combinations are intended either for the treatment of pain or for cough suppression and cold symptom relief. Two products, namely Tussionex Pennkinetic and Tussicaps, that contain hydrocodone in combination with chlorpheniramine maleate are used for the relief of cough and upper respiratory symptoms associated with allergy or a cold in adults and children 6 years of age or older. There are no currently approved products that contain hydrocodone in combination with pseudoephedrine HCl.

CSS Conclusions

In light of the review conducted and described under “CSS Review”, CSS makes the conclusions listed below.

- (b) (4) Oral Solution and REZIRA™ (b) (4) Oral Solution meet the statutory definition for Schedule III control in the Controlled Substances Act.
- The available information in the public domain indicates that hydrocodone alone and in combination with other substances each have an abuse potential.
- The Sponsor has not provided in the NDA specific data pertaining to the abuse potential of (b) (4) Oral Solution and REZIRA™ (b) (4) Oral Solution which are needed for evaluation of safety and labeling.

CSS Recommendations

- The Sponsor needs to fully characterize the abuse potential of both (b) (4) Oral Solution and REZIRA™ (b) (4) Oral Solution, specifically to evaluate how the

addition of the nonnarcotic components (chlorpheniramine and pseudoephedrine) affects the abuse potential of the products relative to hydrocodone alone which is listed as a Schedule II substance in the CSA.

- Therefore the Sponsor should assess the abuse potential and actual abuse of the drug products. Such assessments are necessary to fully determine the appropriate scheduling and safety profile of these products.
- CSS will review protocols and provide comments to the Sponsor prior to beginning studies.

CSS Review

Abuse Potential of (b) (4) Oral Solution and REZIRA (b) (4) Oral Solution

CSS is not aware of any products that are currently marketed and are formulated similar to that of (b) (4) Oral Solution and REZIRA (b) (4) Oral Solution. According to “Clinical Pharmacology Online” the products (b) (4) did not have approved NDAs and not marketed. (b) (4)

The Sponsor utilized post-marketing data and labeling information for Hycodan and Tussionex to indicate that (b) (4) Oral Solution and REZIRA (b) (4) Oral Solution have an abuse potential. No preclinical or clinical studies of abuse potential were conducted on the products and provided in the NDAs submitted by the Sponsor.

With the exception of an FDA Public Health Advisory entitled “Important Information for the Safe Use of Tussionex Pennkinetic Extended-Release Suspension” suggesting some misuse of Tussionex, CSS has not found specific abuse related information regarding hydrocodone in combination with chlorpheniramine and/or pseudoephedrine. In order to evaluate the possible abuse potential of (b) (4) Oral Solution and REZIRA (b) (4) Oral Solution, CSS has examined information relevant to hydrocodone, (including hydrocodone combination products), and to chlorpheniramine and pseudoephedrine.

The information reviewed by CSS predicts that (b) (4) Oral Solution and REZIRA (b) (4) Oral Solution does have an abuse potential and as such will be associated with abuse, misuse, overdoses and the development of physical dependence with possible severe withdrawal syndrome. In addition, the combination of hydrocodone and chlorpheniramine may lead in particular to adverse effects associated with central nervous system depression. With regard to potential abuse and misuse of these products there is an increased concern regarding safety and proper labeling.

Hydrocodone

Both preclinical and clinical studies show that hydrocodone has abuse potential. Hydrocodone as the individual substance has a high potential for abuse and is in Schedule II of the Controlled Substances Act.

Preclinical studies provide evidence of a potential for abuse of hydrocodone. Eddy and Reid (1934) showed that repeated administration of hydrocodone produced dependence in dogs and monkeys. In two studies using rats, hydrocodone shows complete stimulus generalization to fentanyl (Meert and Vermeirsch, 2005) and to morphine (Tomkins et al., 1997). Hydrocodone also maintains intravenous self-administration behavior in rats (Tomkins et al., 1997), thereby demonstrating reinforcing efficacy.

Clinical and epidemiological reports and controlled clinical abuse liability studies attest to the potential for abuse of hydrocodone either alone or in combination with other substances. Early clinical studies document the abuse and addiction of hydrocodone in individuals given hydrocodone either for pain or as an antitussive (for review, see Eddy et al., 1957). Nonmedical use, including abuse, of hydrocodone containing products is also documented in a number of epidemiological reports including reports utilizing data from the Drug Abuse Warning Network (DAWN) and the National Survey on Drug Use and Health (NSDUH) (Hughes et al., 2007; Becker et al., 2008; Butler et al., 2008; Havens et al., 2008; Kelly et al., 2008; Wu et al., 2008).

One noncontrolled study (Fraser and Isbell, 1950) and three controlled abuse liability clinical studies (Zacny, 2003; Zacny et al., 2005; Walsh et al., 2008) using subjects with a history of drug abuse demonstrate that hydrocodone either alone or in combination with acetaminophen or with homatropine (Hycodan) produces subjective reinforcing effects similar to those of other opioids and that are predictive of abuse liability.

CSS has also examined data concerning hydrocodone derived from DAWN and NSDUH. According to DAWN, in 2007 there were an estimated 65,734 emergency department episodes involving the nonmedical use, including abuse, of hydrocodone combination products. According to NSDUH, in 2007, an estimated 21,335,000 individuals reported the nonmedical use of hydrocodone products at least once in their lifetime.

Chlorpheniramine

Chlorpheniramine is a first generation histamine antagonist associated with an abuse potential. It displays stimulus generalization to cocaine (Suzuki et al., 1997; Zacny, 1989) but not to morphine (Suzuki et al., 1997). It also maintains intravenous self-administration behavior in Rhesus monkeys at a level consistent with limited reinforcing efficacy (Beardsley and Balster, 1992). Further evidence of reinforcing efficacy is the ability of chlorpheniramine to evoke conditioned place preference in laboratory animals (Suzuki et al., 1999; Zimmermann et al., 1999; Hasenohrl et al., 2001) which is antagonized by dopamine 1 receptor antagonists (Suzuki et al., 1999). Suzuki et al. (1990) show that chlorpheniramine significantly potentiates the conditioned place

preference evoked by the opioid, dihydrocodeine, thereby suggesting a potentiation of the reinforcing efficacy of the opioid. Chlorpheniramine is also reported to produce effects on dopamine neurotransmission consistent with that of drugs of abuse (Tanda et al., 2008).

Information on abuse and misuse of chlorpheniramine maleate is limited. Recently, Mahanta et al. (2008), reported that in the Mumbai/Thane district of India, heroin (99%) and avil (chlorpheniramine maleate) (87%) were the two main drugs injected by intravenous drug abusers. In Japan, abuse of an over-the-counter antitussive product containing dihydrocodeine, chlorpheniramine, methylephedrine and caffeine is reported (Murao et al., 2008, Tani et al., 1984). The extent to which chlorpheniramine contributes to the abuse of this product is not clear. However, in preclinical studies chlorpheniramine is shown to potentiate the reinforcing properties of dihydrocodeine in a conditioned place preference study (Suzuki et al., 1990) and to suppress development of physical dependence to dihydrocodeine (Suzuki et al., 1988). Finally, in recent years abuse of Coricidin HBP tablets containing chlorpheniramine in combination with dextromethorphan is reported to be abused, particularly among adolescents (Bryner et al., 2006; Dickerson et al., 2008). The extent to which chlorpheniramine contributes to the abuse of the product is not known and has not been studied.

Support for the idea that a first generation antihistamine combined with an opioid can provoke abuse is evident in the case of pentazocine combined with the first generation antihistamine, tripelemnamine. Particularly in the 1970s, this combination, sold illegally as “T’s and Blues” was widely abused by heroin addicts (Lahmeyer and Steingold, 1980; Poklis and Whyatt, 1980; Debard and Jagger, 1981). More recently, heroin combined with the first generation antihistamine, diphenhydramine, as well as acetaminophen, was distributed in the illicit drug market under the street name of “Cheese” in the United States, particularly in the Southwest (Erowid website).

Pseudoephedrine

Pseudoephedrine is considered to have a relatively low potential for abuse. At high doses pseudoephedrine generalizes to amphetamine (Tongjaroenbuangam et al., 1998). Isomers of pseudoephedrine display weak reinforcing efficacy as evidenced by their ability at high doses to maintain intravenous self-administration behavior in Rhesus monkeys and to interact with the dopamine transporter (Wee et al., 2004). There is little information on actual abuse of pseudoephedrine.

Scheduling of (b) (4) Oral Solution and REZIRA™ (b) (4) Oral Solution

While hydrocodone substance is in Schedule II of the Controlled Substances Act, hydrocodone combination products currently approved for use in the United States are placed in Schedule III, pursuant to 21 U.S.C. 812(c)(Schedule III)(d)(4). This provision of the CSA specifies that unless specifically excepted or unless listed in another schedule, any material, compound, mixture, or preparation is in Schedule III, if it contains not more

than 300 milligrams of hydrocodone per 100 milliliters or not more than 15 milligrams per dosage unit, with one or more active, nonnarcotic ingredients in recognized therapeutic amounts. Both (b) (4) Oral Solution and REZIRA (b) (4) Oral Solution meet the requirements of this provision for Schedule III control

For both (b) (4) Oral Solution and REZIRA (b) (4) Oral Solution, the concentration of hydrocodone is (b) (4). Chlorpheniramine and pseudoephedrine are nonnarcotics substances as they do not fit the definition for a “narcotic drug” found in 21 U.S.C. 802(17).

Finally, (b) (4) Oral Solution and REZIRA (b) (4) Oral Solution each meet the criterion that the nonnarcotic ingredients are present in recognized therapeutic amounts. Information from the product formulation and dosage regimen, as well as from the OTC Drug Monograph for pseudoephedrine HCl (21 CFR 341.20(a)(2) and 21 CFR 341.80(d)(1)(ii)) and for chlorpheniramine maleate (21 CFR 341.12(c) and 21 CFR 341.72(d)(3)) indicate that the pseudoephedrine HCl and chlorpheniramine maleate present in (b) (4) Oral Solution are at therapeutic doses as a nasal decongestant and antihistamine, respectively. Information from the product formulation and dosage regimen, as well as from the OTC Drug Monograph (21 CFR 341.20 and 21 CFR 341.80(d)(1)(ii)), indicate that pseudoephedrine HCl present in REZIRA (b) (4) Oral Solution is at a therapeutic dose as a nasal decongestant.

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/s/

JAMES M TOLLIVER
09/03/2009

LORI A LOVE
09/03/2009

MICHAEL KLEIN
09/03/2009

NDA/BLA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

Application Information		
NDA # 22-442 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Rezira ^(b) ₍₄₎ Established/Proper Name: hydrocodone and pseudoephedrine Dosage Form: oral solution Strengths: 5 ml contains hydrocodone 5mg and pseudoephedrine 60mg		
Applicant: Cypress Pharmaceuticals, Inc. Agent for Applicant (if applicable): William Putnam, Ph.D., R.A.C. Beckloff Associates, Inc.		
Date of Application: November 7, 2008 Date of Receipt: November 10, 2008 Date clock started after UN:		
PDUFA Goal Date: September 10, 2009	Action Goal Date (if different): September 4, 2009	
Filing Date: January 9, 2009 Date of Filing Meeting: December 15, 2008		
Chemical Classification: (1,2,3 etc.) (original NDAs only) 4		
Proposed Indication(s): ^(b) ₍₄₎ relief of cough, for the ^(b) ₍₄₎ <div style="background-color: #cccccc; height: 15px; width: 100%;"></div> relief of nasal congestion due to the common cold		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: <i>Refer to Appendix A for further information.</i>	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical disease Priority review voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/> Resubmission after refuse to file? <input type="checkbox"/>		
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify	

Other:	clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (if OTC product):	
List referenced IND Number(s): 102,177	
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ora/compliance_ref/aiplist.html</i> If yes, explain: If yes, has OC/DMPQ been notified of the submission? Comments:	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fee Status Comments:	<input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	
Exclusivity	

<p>Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</i></p> <p>If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES # years requested: 3 <input type="checkbox"/> NO
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<input checked="" type="checkbox"/> Not applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
<ol style="list-style-type: none"> 1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? 2. Is the application for a duplicate of a listed drug whose only difference is that 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 21 CFR 314.54(b)(1)). 3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? 	<input type="checkbox"/> Not applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

<p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p>			
<p>4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</p>		<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO	
<p>If yes, please list below:</p>			
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>			
Format and Content			
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> <p>Comments:</p>		<input type="checkbox"/> All paper (except for COL) <input type="checkbox"/> All electronic <input checked="" type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)	
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p> <p>All modules, as well as administrative forms, have been submitted electronically.</p>			
<p>If electronic submission: <u>paper</u> forms and certifications signed (non-CTD) or <u>electronic</u> forms and certifications signed (scanned or digital signature)(CTD)?</p> <p><i>Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> <p>Comments: Form 3542a was not submitted</p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	
<p>If electronic submission, does it follow the eCTD guidance? http://www.fda.gov/cder/guidance/7087rev.pdf</p> <p>If not, explain (e.g., waiver granted):</p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	

<p>Form 356h: Is a signed form 356h included?</p> <p><i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Index: Does the submission contain an accurate comprehensive index?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Controlled substance/Product with abuse potential:</p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BLAs/BLA efficacy supplements only:</p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Patent Information (NDAs/NDA efficacy supplements only)	
<p>Patent information submitted on form FDA 3542a?</p> <p>Comments:</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
Debarment Certification	
<p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><i>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...”</i></p> <p>Comments:</p>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)</p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<p><input checked="" type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Financial Disclosure	
<p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Pediatrics	
<p><u>PREA</u></p>	
<p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	
<p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES</p> <p><input checked="" type="checkbox"/> NO</p>
<p>If no, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • <i>If no, request in 74-day letter.</i> • If yes, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) 	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p>Comments: Application specified 21 CFR 314.55(c)(2)</p>	

<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i></p> <p>Comments:</p>	<p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>
Prescription Labeling	
<p>Check all types of labeling submitted.</p> <p>Comments:</p>	<p><input type="checkbox"/> Not applicable <input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use <input type="checkbox"/> MedGuide <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)</p>
<p>Is electronic Content of Labeling submitted in SPL format?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>Package insert (PI) submitted in PLR format?</p> <p>If no, was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>MedGuide or PPI (plus PI) consulted to OSE/DRISK? (<i>send WORD version if available</i>)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>REMS consulted to OSE/DRISK?</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>

OTC Labeling	
<p>Check all types of labeling submitted.</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
<p>Is electronic content of labeling submitted?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Are annotated specifications submitted for all stock keeping units (SKUs)?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>If representative labeling is submitted, are all represented SKUs defined?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?</p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Meeting Minutes/SPA Agreements	
<p>End-of Phase 2 meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO
<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO
<p>Any Special Protocol Assessment (SPA) agreements?</p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 15, 2008

NDA/BLA #: 22-442

PROPRIETARY/ESTABLISHED NAMES: Rezira ^(b)₍₄₎

APPLICANT: Cypress Pharmaceuticals

BACKGROUND: 505(b)(2) application for a marketed unapproved drug

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Philantha M. Bowen	Y
	CPMS/TL:	Sandy Barnes	N
Cross-Discipline Team Leader (CDTL)	Wei Qiu,		Y
Clinical	Reviewer:	Theresa Michele	Y
	TL:	Sally Seymour	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OSE	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Sandra Suarez	N
	TL:	Wei Qiu	Y
Biostatistics	Reviewer:	Same as TL	
	TL:	Qian Li	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Virgil Whitehurst	Y
	TL:	Timothy Robison	Y
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Xiaobin Shen	Y
	TL:	Prasad Peri Ali Al-Hakim	Y N
Facility (<i>for BLAs/BLA supplements</i>)	Reviewer:		
	TL:		
Microbiology, sterility (<i>for NDAs/NDA efficacy supplements</i>)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Other reviewers			

OTHER ATTENDEES:

505(b)(2) filing issues? If yes, list issues:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
Per reviewers, are all parts in English or English translation? If no, explain:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p>Electronic Submission comments</p> <p>List comments: Administrative forms and modules are all electronic</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p> <p>Product not BE, thus no DSI will be requested; See Clinical Pharmacology filing review dated 1/9/09</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> • 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? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE

<p>Comments:</p>	<input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Establishment(s) ready for inspection? Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Sterile product? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

If yes, was Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)	<input type="checkbox"/> YES <input type="checkbox"/> NO
FACILITY (BLAs only) Comments:	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Badrul A. Chowdhury, M.D., Ph.D. GRMP Timeline Milestones: Filing Meeting 12/15/08 Filing Date 1/9/09 74 Day Letter 1/23/09 MCR Meeting 3/31/09 Primary Reviews Due 7/10/09 Secondary Reviews Due 7/23/09 Full Labeling Meeting 6/5/09 WU Meeting 6/29/09 Labeling T-con w/sponsor 8/5/09 PDUFA Date 9/10/09 Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF action, notify everybody who already received a consult request, OSE PM., and

	Product Quality PM. Cancel EER/TBP-EER.
<input type="checkbox"/>	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If BLA or priority review NDA, send 60-day letter.
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original 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 written 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) 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, or
- (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.)

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) 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, and.
- (3) 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) 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, or
- (3) 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 OND ADRA or OND IO.

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

/s/

PHILANTHA M BOWEN
07/29/2009

SANDRA L BARNES
08/05/2009

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Pulmonary and Allergy Products

Application Number: NDA 22-442

Name of Drug: Rezira-^(b)₍₄₎ (hydrocodone and pseudoephedrine) oral solution

Applicant: Cypress Pharmaceuticals

Material Reviewed:

Submission Date(s): November 7, 2008

Receipt Date(s): November 10, 2008

Submission Date of Structure Product Labeling (SPL): November 7, 2008

Type of Labeling Reviewed: Package Insert

Background and Summary

On November 7, 2008, Cypress Pharmaceuticals submitted a supplemental New Drug Application for ReziraTM ^(b)₍₄₎ for the ^(b)₍₄₎ relief of cough and for the temporary relief of nasal congestion due to the common cold.

The proposed labeling text for Rezira-^(b)₍₄₎ was provided in SPL, including carton and container labels. Draft labeling text was submitted in Word format (.doc) for review on November 7, 2008.

Review

The WORD and SPL version of the proposed labeling in the new PLR format was reviewed using the Label Review Tool provided by SEALD.

Address the identified deficiency/issue and re-submit the labeling. This updated version of labeling will be used for further labeling discussions.

The following comments pertain to the Highlights and the Full Prescribing Information-Details

section of the product label:

Do not use the “TM” or “R” symbols after the drug names in the Highlights section of the label. In addition, remove the “TM” symbols following the drug name in the detailed Full Prescribing Information (FPI). These symbols may be used once upon first use in the FPI. This format is recommended because symbols may not appear in the SPL version of labeling and the WORD version should match the SPL version as much as possible.

Recommendations

Comment/recommendation for the proposed labeling have been identified and will be conveyed to the applicant in the 74-day letter.

Philantha M. Bowen
Regulatory Project Manager
CDER, OND, ODE II

Supervisory Comment/Concurrence:

Sandy Barnes
Chief, Project Management Staff
CDER, OND, ODE II

Drafted: Bowen/ January 12, 2009

Revised/Initialed: Barnes/ July 23, 2009

Finalized: Bowen/ July 28, 2009

Filename: N 22-442 (000) PM PLR Review

CSO LABELING REVIEW OF PLR FORMAT

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

/s/

PHILANTHA M BOWEN
07/28/2009

SANDRA L BARNES
08/05/2009