

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022439Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

### 1.3.5.2 Patent Certification

#### Certification of No Relevant Patents

Pursuant to 21 U.S.C. § 355(b)(2)(A) of the Federal Food, Drug, and Cosmetic Act, and 21 CFR 314.50(i)(1)(ii), in the opinion and to the best knowledge of Cypress Pharmaceutical, Inc., there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim of such drug or drugs.



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Robert L. Lewis II  
Director of Product Development  
Cypress Pharmaceutical, Inc.  
Madison, MS

November 06 2008

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Date

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

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

NDA NUMBER

022439

NAME OF APPLICANT / NDA HOLDER

Cypress Pharmaceutical, Inc.

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

TRADE NAME (OR PROPOSED TRADE NAME)

(b) (4) Oral Solution

ACTIVE INGREDIENT(S)

Hydrocodone Bitartrate, USP  
Chlorpheniramine Maleate, USP  
Pseudoephedrine Hydrochloride, USP

STRENGTH(S)

5 mg/4 mg/60 mg per 5 mL

DOSAGE FORM

Solution

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).

Within thirty (30) days after approval of an NDA, or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

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

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

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

**1. GENERAL**

a. United States Patent Number

b. Issue Date of Patent

c. Expiration Date of Patent

d. Name of Patent Owner

Address (of Patent Owner)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

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

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

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

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

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No

2.6 Does the patent claim only an intermediate?  Yes  No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

**Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:**

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

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

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

**5. No Relevant Patents**

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

**6 Declaration Certification**

6.1 **The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.**  
**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below) Date Signed  
1/28/2009

*Janet K. DeLeon*

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

Check applicable box and provide information below.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Janet K. DeLeon, R.A.C. Director of Product Development Cypress Pharmaceutical, Inc.	
Address 135 Industrial Blvd.	City/State Madison, MS
ZIP Code 39110	Telephone Number 800-856-4393
FAX Number (if available) (601) 853-1567	E-Mail Address (if available) jdeleon@cypressrx.com

## EXCLUSIVITY SUMMARY

NDA # 22439

SUPPL #

HFD # 570

Trade Name Zutripro

Generic Name hydrocodone, chlorpheniramine, and pseudoephedrine

Applicant Name Cypress Pharmaceuticals, Inc.

Approval Date, If Known June 8, 2011

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

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

YES  NO

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

#### 505(b)(2)

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

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

**The development program for this application is based on demonstration of bioequivalence to the reference ingredients of the combination product. Since hydrocodone is not a monograph product, clinical studies would normally be required to support a combination product containing hydrocodone and other active ingredients in order to demonstrate the contribution of each component to the combination product as required by regulation (21CFR 300.50). However, because of the prior regulatory precedent of approving Tussionex Pennkinetic (the combination of hydrocodone and chlorpheniramine) with clinical pharmacology data only, combination products containing hydrocodone and other**

**monograph active ingredients that are permitted monograph combinations can be developed under a clinical pharmacology program only. Therefore, clinical efficacy and safety studies may not be necessary to support this combination product provided that the applicant carries out a satisfactory clinical pharmacology program.**

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

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

**3 years**

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

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

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

2. Is this drug product or indication a DESI upgrade?

YES  NO

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

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this

particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

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

NDA#

NDA#

NDA#

## 2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

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

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

## **PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation

duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

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

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1  
IND # YES  ! NO   
! Explain:

Investigation #2  
IND # YES  ! NO   
! Explain:



Date: June 2, 2011

Name of Office/Division Director signing form: Lydia Gilbert-McClain, MD  
Title: DPARP, Deputy Division Director

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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PHILANTHA M BOWEN  
06/09/2011

LYDIA I GILBERT MCCLAIN  
06/09/2011  
Deputy Division Director

**PEDIATRIC PAGE**  
**(Complete for all filed original applications and efficacy supplements)**

NDA/BLA#: 22-439 Supplement Number: \_\_\_\_\_ NDA Supplement Type (e.g. SE5): \_\_\_\_\_  
Division Name: DPARP PDUFA Goal Date: \_\_\_\_\_ Stamp Date: December 10, 2009  
June 11, 2010

Proprietary Name: (b) (4) (proposed)

Established/Generic Name: hydrocodone, chlorpheniramine, and pseudoephedrine

Dosage Form: Oral Solution

Applicant/Sponsor: Cypress Pharmaceuticals, Inc.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) \_\_\_\_\_
- (2) \_\_\_\_\_
- (3) \_\_\_\_\_
- (4) \_\_\_\_\_

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Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 3

**(Attach a completed Pediatric Page for each indication in current application.)**

**Indication #1:** Relief of cough and nasal congestion associated with common cold

**Q1:** Is this application in response to a PREA PMR? Yes  Continue  
No  Please proceed to Question 2.

If Yes, NDA/BLA#: \_\_\_\_\_ Supplement #: \_\_\_\_\_ PMR #: \_\_\_\_\_

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
- No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

**Q2:** Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW  active ingredient(s) (includes new combination);  indication(s);  dosage form;  dosing regimen; or  route of administration?\*

(b)  No. PREA does not apply. **Skip to signature block.**

**\* Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

**Q3:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

**Q4:** Is there a full waiver for all pediatric age groups for this indication (check one)?

Yes: (Complete Section A.)

No: Please check all that apply:

- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
- Deferred for some or all pediatric subpopulations (Complete Sections C)
- Completed for some or all pediatric subpopulations (Complete Sections D)
- Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
- Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**

Reason(s) for full waiver: **(check, and attach a brief justification for the reason(s) selected)**

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

*Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).*

		Reason (see below for further detail):					
		minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	0 yr. __ mo.	5 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver **(check reason** corresponding to the category checked above, and **attach a brief**

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpms@fda.hhs.gov](mailto:cderpms@fda.hhs.gov)) OR AT 301-796-0700.

**justification):**

## # Not feasible:

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_

## \* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

## † Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

## Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

 Justification attached.

*or those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.*

**Section C: Deferred Studies (for selected pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
X	Other	6 yr. __ mo.	17 yr. 11 mo.	X	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): Complete PK study by 12/31/2012; Complete safety study by 12/31/2013							

Are the indicated age ranges (above) based on weight (kg)? X No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage? X No;  Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	<input type="checkbox"/> yr. __ mo.	<input type="checkbox"/> yr. <input type="checkbox"/> mo.
<input type="checkbox"/>	Other	<input type="checkbox"/> yr. __ mo.	<input type="checkbox"/> yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as*

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

*If there are additional indications, please complete the attachment for each one of those indications.*

*Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.*

This page was completed by:

{See appended electronic signature page}

\_\_\_\_\_  
Regulatory Project Manager

(Revised: 6/2008)

**NOTE: If you have no other indications for this application, you may delete the attachments from this document.**

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

**Indication #2: Relief of symptoms including nasal congestion associated with upper respiratory allergies**

Q1: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - Deferred for some or all pediatric subpopulations (Complete Sections C)
  - Completed for some or all pediatric subpopulations (Complete Sections D)
  - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**Reason(s) for full waiver: **(check, and attach a brief justification for the reason(s) selected)**

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
	minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	0 yr. __ mo.	5 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

# Not feasible:

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_

\* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpmhs@fda.hhs.gov](mailto:cderpmhs@fda.hhs.gov)) OR AT 301-796-0700.

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

**ction C: Deferred Studies (for some or all pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received	
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input checked="" type="checkbox"/> Other	6 yr. __ mo.	17 yr. 11 mo.	X	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): Complete PK study by 12/31/2012; Complete safety study by 12/31/2013							

Are the indicated age ranges (above) based on weight (kg)?      X No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?      X No;  Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	<input type="checkbox"/> yr. __ mo.	<input type="checkbox"/> yr. <input type="checkbox"/> mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

**If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.**

**This page was completed by:**

{See appended electronic signature page}

\_\_\_\_\_  
**Regulatory Project Manager**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700**

Revised: 6/2008)

**NDA 22-439**

**Section B: Partially Waived Studies**

**Justification:** Hydrocodone is contraindicated in patients under 6 years of age. Deaths due to respiratory depression have been reported in pediatric patients under 6 years of age. Since the combination product contains hydrocodone, it would also be contraindicated in patients under 6 years of age.

### 1.3.3 Debarment Certification

Cypress Pharmaceutical, Inc. (Cypress), 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 (the Act) in connection with this application.

Cypress certifies that, during the previous 5 years, it has not sustained a conviction that is described in Sections 306(a) or (b) of the Act. In addition, no person affiliated with Cypress nor affiliated persons responsible for the development or submission of this application have been convicted of an offense described in Sections 306(a) or (b) of the Act.

Furthermore, Cypress agrees to notify FDA of any changes in status of any employee with respect to Sections 306(a) or (b) of the Act.

Due diligence for this purpose includes the keeping of a current list of companies and individuals debarred by FDA. Notice of debarment is published in the *Federal Register*, and FDA issues a quarterly list. In addition, we have a questionnaire for new executive hires and certification statements for outside contractors.



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Robert L. Lewis II  
Director of Product Development  
Cypress Pharmaceutical, Inc.  
Madison, MS

November 06 2008

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Date

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 22439 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Zutripro Established/Proper Name: hydrocodone, chlorpheniramine, and pseudoephedrine Dosage Form: Oral Solution		Applicant: Cypress Pharmaceutical Agent for Applicant (if applicable):
RPM: Philantha Bowen		Division: DPARP
<p><b>NDA:</b>            NDA Application Type:    <input type="checkbox"/> 505(b)(1)    <input checked="" type="checkbox"/> 505(b)(2)            Efficacy Supplement:    <input type="checkbox"/> 505(b)(1)    <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><b>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</b>            Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s):  <i>NDA 5213 Hycodan</i>  <i>NDA 19111 Tussionex *</i>  <i>NDA 21369 Codeprex *</i>  <i>NDA 21082 Tavist Allergy*</i>  <i>NDA 21441 Advil Allergy Simus*</i></p> <p><i>* 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.</i></p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><i>New combination product</i></p> <p>If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature.  <input type="checkbox"/> This application relies on a final OTC monograph.  <input type="checkbox"/> Other (explain)</p> <p><b><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input checked="" type="checkbox"/> No changes    <input type="checkbox"/> Updated    Date of check: June 8, 2011</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p>
❖ Actions		

<sup>1</sup> The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.



❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input checked="" type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes  No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes  No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "**No**," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes  No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

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

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
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**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>3</sup>	9/17/09; 6/11/10; 6/8/11
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) CR: 9/18/09 CR: 6/11/10 AP: 6/8/11
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	May 17, 2011
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	December 8, 2010
<ul style="list-style-type: none"> <li>Example of class labeling, if applicable</li> </ul>	

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> <li>❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)</li> </ul>	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> <li>• Original applicant-proposed labeling</li> <li>• Example of class labeling, if applicable</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	FPL: May 27, 2011
<ul style="list-style-type: none"> <li>❖ Proprietary Name           <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> </ul> </li> </ul>	1/6/09; 1/11/10; 5/4/10; 5/7/10; 7/27/10; 2/24/11  <u>Reviews:</u> 12/29/09; 7/22/10; 2/24/11; 5/25/11
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input checked="" type="checkbox"/> RPM 8/5/09; 6/18/10; 5/5/11 <input checked="" type="checkbox"/> DMEPA 5/10/10; 5/3/11; 6/2/11 <input type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC 5/10/10; 5/4/11 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews: <u>Nonclinical:</u> 5/9/11  <u>Meetings:</u> 6/16/09; 4/13/10; 4/25/11
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	8/5/9 <input type="checkbox"/> Not a (b)(2) <input type="checkbox"/> Not a (b)(2) 9/17/09; 4/27/10; 5/27/10; addendum 5/27/10; 5/24/11; 6/2/11
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents  <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a> </li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP           <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action

<sup>4</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>Date reviewed by PeRC <u>5/26/10, PeRC Summary 6/9/10; 5/3/11</u> If PeRC review not necessary, explain: _____</li> <li>Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent ( <i>include certification</i> )	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications ( <i>letters (except action letters), emails, faxes, telecons</i> )	11/24/08; 1/6/09; 1/16/09; 2/23/09; 4/30/09; 6/3/09; 6/9/09; 12/29/09; 3/26/10; 5/5/10; 5/12/10; 12/23/10; 1/31/11; 4/14/11; 4/28/11; 5/16/11; 5/25/11; and 5/27/11
❖ Internal memoranda, telecons, etc.	2/29/08; 4/8/09; 7/2/10
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>Regulatory Briefing (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg 6/12/09
<ul style="list-style-type: none"> <li>If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> <li>Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)</li> </ul>	Pre-IND 1/14/08
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>Date(s) of Meeting(s)</li> <li>48-hour alert or minutes, if available (<i>do not include transcript</i>)</li> </ul>	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 9/18/09; 6/11/10; 6/8/11
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 5/27/11
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input type="checkbox"/> None 2
<b>Clinical Information<sup>5</sup></b>	
❖ Clinical Reviews	
<ul style="list-style-type: none"> <li>Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>	See DD memo's (9/18/09 & 6/11/10) CDTL (5/27/11)
<ul style="list-style-type: none"> <li>Clinical review(s) (<i>indicate date for each review</i>)</li> </ul>	12/19/08; 7/21/09; 5/26/10; 1/27/11; 5/13/11
<ul style="list-style-type: none"> <li>Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	5/13/11; pg 17
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None

<sup>5</sup> Filing reviews should be filed with the discipline reviews.

❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input type="checkbox"/> Not applicable CSS review 9/3/09; 9/11/09; OSE review 8/26/09
❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input checked="" type="checkbox"/> None requested
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4/21/11
Statistical Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None See concurrence on CP reviews
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 1/9/09; 7/20/09; 5/3/10; 5/25/10; 5/12/11
❖ DSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input type="checkbox"/> None 5/5/10; 5/24/10; 4/14/11
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 6/22/09; 5/11/10; 5/17/11
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 6/17/09; 5/3/10; 5/9/11
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 5/27/09
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input checked="" type="checkbox"/> None requested

<b>Product Quality</b>		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> None 7/14/09; 5/18/11
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		<input type="checkbox"/> None 12/11/08; 7/8/09; 8/31/09; 4/21/10; 4/12/11
❖ Microbiology Reviews		<input type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>		3/16/09
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		<input type="checkbox"/> None Nonclinical: 5/20/09; 2/22/10
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		7/8/09
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		
❖ Facilities Review/Inspection		
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>6</sup>)</i>		Date completed: 8/31/09 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>		<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

<sup>6</sup> I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

## Appendix to Action Package Checklist

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

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a 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) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

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

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

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

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

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

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

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

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/s/  
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PHILANTHA M BOWEN  
06/08/2011



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II**

**Memorandum of Facsimile Correspondence**

Date: May 27, 2011

To: Janet DeLeon  
Director of Product Development

Company: Cypress Pharmaceuticals

Fax: 913-681-0669

Phone: 913-681-0667

From: Philantha Bowen, MPH, RN  
Senior Regulatory Management Officer  
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: NDAs 22439 & 22442 - Request for Revised PMR Timeline

# of Pages including cover: 3

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Thank you.

**NDA 22439 (Zutripro)**  
**NDA 22442 (Rezira)**  
**Cypress Pharmaceuticals, Inc.**

Reference is made to your submissions dated May 6 and 19, 2010, to NDAs 22439 and 22442, Zutripro and Rezira, respectively. We acknowledge your prior agreement to conduct post-marketing pediatric studies. We are requesting that you submit a revised milestone timeline for the pharmacokinetic and safety studies for this post-marketing requirement (PMR).

- Use the following schedule for both studies:

**PMR Schedule Milestones:**

Final protocol Submission Date: MM/DD/YYYY (if applicable)

Study/Clinical trial Completion Date: MM/DD/YYYY (if applicable)

Final Report Submission Date: MM/DD/YYYY

Submit your agreement to conduct the post-marketing requirement officially to the NDAs and forward a courtesy to me via email. In the submissions, include the PMR milestone schedule. We request that you submit a response by Tuesday May 31, 2011.

If you should have any questions, contact me at 301-796-2466.

Sincerely,

*{See appended electronic signature page}*

Philantha M. Bowen, MPH, RN  
Sr. Regulatory Project Management Officer  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Drafted: Bowen/May 27, 2011

Clearance: Barnes/May 27, 2011

Finalized by: Bowen/May 27, 2011

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/s/  
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PHILANTHA M BOWEN  
05/27/2011



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** May 25, 2011

<b>To:</b> Janet DeLeon	<b>From:</b> Philantha Bowen
<b>Company:</b> Cypress Pharmaceuticals	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 913-681-0669	<b>Fax number:</b> 301-796-9718
<b>Phone number:</b> 913-681-0667	<b>Phone number:</b> 301-796-2466

**Subject:** NDAs: 22439 and 22442 Re: FDA Labeling Recommendations – Professional Samples Carton

**Total no. of pages including cover:** 3

**Comments:**

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**Document to be mailed:**  YES  NO

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**NDA 22439 (Zutripro)**  
**NDA 22442(Rezira)**  
**Cypress Pharmaceuticals, Inc.**

Your submissions dated December 8, 2010, to NDAs 22439 and 22442 are under review and we have a request for labeling revisions. These comments are not all-inclusive and we may have additional comments and/or requests as we continue our review of the labels.

We have the following comment regarding the professional samples for both Rezira and Zutripro:

General Comment

1. Limit the fill volume of the professional sample presentations to a 5 mL to minimize the risk of accidental overdose with these products.

Carton Labeling

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

Container Label

4. The 'Professional Sample' statement [REDACTED] (b) (4) [REDACTED] should be oriented horizontally and relocated to the principle display panel to increase its readability.

Submit revised professional sample carton labels incorporating the recommended changes outlined above by May 27, 2011. Submit the labels officially to the NDAs. In addition, please forward a courtesy copy to me via email.

**NDA 22439 (Zutripro)**  
**NDA 22442(Rezira)**  
**Cypress Pharmaceuticals, Inc.**  
Page 2

If there are any questions, contact Philantha Bowen, Senior Regulatory Management Officer, at 301-796-2466.

*{See appended electronic signature page}*

---

Philantha Montgomery Bowen, MPH, RN  
Sr. Regulatory Project Management Officer  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Drafted by: Bowen/May 23, 2011

Clearance: Raggio for Barnes/May 24, 2011  
Griffis/May May 25, 2011

Finalized by: Bowen/May 25, 2011

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/s/  
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PHILANTHA M BOWEN  
05/25/2011

## Bowen, Philantha

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**From:** Duvall Miller, Beth A  
**Sent:** Tuesday, May 24, 2011 4:12 PM  
**To:** Bowen, Philantha  
**Cc:** Ripper, Leah W  
**Subject:** RE: NDAs: 22439 & 22442 - 505(b)(2) clearance follow-up item and clearance

Great, thanks for the speedy follow-up.

Beth

*Beth Duvall-Miller*

Team Leader, Regulatory Affairs Team  
CDER/Office of New Drugs  
Direct Phone Number: (301) 796-0513  
OND IO Phone Number: (301) 796-0700  
Fax: (301) 796-9855

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**From:** Bowen, Philantha  
**Sent:** Tuesday, May 24, 2011 3:46 PM  
**To:** Duvall Miller, Beth A  
**Cc:** Ripper, Leah W  
**Subject:** RE: NDAs: 22439 & 22442 - 505(b)(2) clearance follow-up item and clearance

Hi,

The 356h's have been submitted and received today. I note your comment about the 505b2 clearance for these applications.

Sincerely,

*Philantha*

---

**From:** Duvall Miller, Beth A  
**Sent:** Monday, May 23, 2011 3:44 PM  
**To:** Bowen, Philantha  
**Cc:** Ripper, Leah W  
**Subject:** NDAs: 22439 & 22442 - 505(b)(2) clearance follow-up item and clearance

Please note that this e-mail is for internal FDA use only, and should not be appended to any correspondence, reviews, memos, emails, or meeting minutes nor should it be forwarded directly to industry without my prior agreement.

Hi Philantha,

We discussed your application at today's clearance and have one follow-up item for you.

The applicant still lists the generic Hi-Tech Syrup as the listed drug relied-upon for this application on their 356h form, both the form submitted with the 12/8/10 RS and the most recent submission to this application in general. As noted previously, this application

relies only on Endo Pharm's NDA 005213, Hycodan Syrup. Therefore, Cypress should make this correction on the next (and all future) 356h forms they submit for this pending application. If for some reason they don't plan on any more submissions between now and the PDUFA due date, then at a minimum they need to submit a new 356h form that accurately cites reliance on the correct listed drug.

Assuming the applicant does this, you are cleared for action from a 505(b)(2) perspective.

Beth

*Beth Duvall-Miller*

Team Leader, Regulatory Affairs Team

CDER/Office of New Drugs

Direct Phone Number: (301) 796-0513

OND IO Phone Number: (301) 796-0700

Fax: (301) 796-9855

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**From:** Bowen, Philantha  
**Sent:** Monday, May 16, 2011 4:13 PM  
**To:** Duvall Miller, Beth A  
**Cc:** Ripper, Leah W  
**Subject:** RE: NDAs: 22439 & 22442 - Resubmissions - 505b2 Reassessment Inquiry

Hi,

The memo and 505b2 FRMs were checked into DARRTs on 5/27/10 for both applications. I attached only the memo below.

<< File: 505b2 Memo.pdf >>

Sincerely,

*Philantha*

---

**From:** Duvall Miller, Beth A  
**Sent:** Monday, May 16, 2011 3:59 PM  
**To:** Bowen, Philantha  
**Cc:** Ripper, Leah W; Barnes, Sandy L (CDER); Hill, Carol  
**Subject:** RE: NDAs: 22439 & 22442 - Resubmissions - 505b2 Reassessment Inquiry

Philantha,

In preparing an update for your pending b2s for discussion next week, I have a feeling this memo never made its way into DARRTS, correct?

It looks like Kim had wanted you to check it first for accuracy – do you know if you ever did that? I'm happy to archive it in DARRTS, but wanted to make sure 1) it wasn't already in there (I didn't find it) and 2) you had ok'd it.

Please let me know.

Beth

*Beth Duvall-Miller*

Team Leader, Regulatory Affairs Team  
CDER/Office of New Drugs  
Direct Phone Number: (301) 796-0513  
OND IO Phone Number: (301) 796-0700  
Fax: (301) 796-9855

---

**From:** Quintance, Kim M  
**Sent:** Thursday, May 13, 2010 10:21 AM  
**To:** Bowen, Philantha; Hill, Carol; Barnes, Sandy L (CDER)  
**Cc:** Ripper, Leah W; Duvall Miller, Beth A  
**Subject:** RE: NDAs: 22439 & 22442 - Resubmissions - 505b2 Reassessment Inquiry

Now that I think about it...before I enter this into DARRTS, can you (DPARP) please review it to make sure it is factually accurate?

<< File: N22439\_22442 clearance memo.doc >>

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**From:** Quintance, Kim M  
**Sent:** Thursday, May 13, 2010 10:15 AM  
**To:** Bowen, Philantha; Duvall Miller, Beth A  
**Cc:** Barnes, Sandy L (CDER); Ripper, Leah W; Hill, Carol  
**Subject:** RE: NDAs: 22439 & 22442 - Resubmissions - 505b2 Reassessment Inquiry

Philantha,

Sorry for the delay. Heads up that I will be entering the memo into DARRTS shortly.

Kim

---

**From:** Quintance, Kim M  
**Sent:** Tuesday, April 27, 2010 3:32 PM  
**To:** Bowen, Philantha; Duvall Miller, Beth A  
**Cc:** Barnes, Sandy L (CDER); Ripper, Leah W; Hill, Carol  
**Subject:** RE: NDAs: 22439 & 22442 - Resubmissions - 505b2 Reassessment Inquiry

Philantha,

In follow-up to our (b)(2) clearance meeting yesterday, your applications are again cleared for action (approval) from a (b)(2) perspective. At the request of ORP/OCC, I have drafted a memo to clarify that we are not relying upon the finding of S&E for Hi-Tech Syrup even though it was added by the applicant as part of the resubmission. I will send this to you and archive in DARRTS once they have cleared it.

Regards,  
Kim

---

**From:** Quintance, Kim M  
**Sent:** Friday, April 23, 2010 1:56 PM  
**To:** Bowen, Philantha; Duvall Miller, Beth A  
**Cc:** Barnes, Sandy L (CDER); Ripper, Leah W; Hill, Carol  
**Subject:** RE: NDAs: 22439 & 22442 - Resubmissions - 505b2 Reassessment Inquiry

I agree - whew!

---

**From:** Bowen, Philantha

**Sent:** Friday, April 23, 2010 1:12 PM  
**To:** Quaintance, Kim M; Duvall Miller, Beth A  
**Cc:** Barnes, Sandy L (CDER); Ripper, Leah W; Hill, Carol  
**Subject:** RE: NDAs: 22439 & 22442 - Resubmissions - 505b2 Reassessment Inquiry

Whew! Thanks!

**Philantha**

---

**From:** Quaintance, Kim M  
**Sent:** Friday, April 23, 2010 1:11 PM  
**To:** Bowen, Philantha; Duvall Miller, Beth A  
**Cc:** Barnes, Sandy L (CDER); Ripper, Leah W; Hill, Carol  
**Subject:** RE: NDAs: 22439 & 22442 - Resubmissions - 505b2 Reassessment Inquiry

Philantha,

I still plan to discuss this on Monday, but the good news is that this may not trigger MMA after all. The new product that they cite reliance upon was approved as an ANDA (I didn't read it closely enough) so that changes everything.

Stay tuned!

---

**From:** Bowen, Philantha  
**Sent:** Thursday, April 22, 2010 12:55 PM  
**To:** Quaintance, Kim M; Duvall Miller, Beth A  
**Cc:** Barnes, Sandy L (CDER); Ripper, Leah W; Hill, Carol  
**Subject:** RE: NDAs: 22439 & 22442 - Resubmissions - 505b2 Reassessment Inquiry

Hi Kim,

Thanks!

The PDUFA date is June 11, 2010.

Before clarifying your question, I would like to state my interpretation of your comment. For 505b2 NDAs that receive a CR action, the RLDs, in general, should be the same in the resubmissions as listed in the original application. Thus, RLD's are not cumulative, meaning one cannot simply add or remove a RLD in a resubmitted 505b2 application.

If my thinking is correct, my response is yes. The Hi-Tech Syrup ( ANDA 40613) was not mentioned in the original submission. In the resubmissions, Hycodan is not on the 356h, however it is mentioned in the annotated labeling. Hycodan has been d'c from marketing and the resubmissions now rely on Hi-Tech Syrup.

Sincerely,  
**Philantha**

---

**From:** Quaintance, Kim M  
**Sent:** Thursday, April 22, 2010 12:28 PM  
**To:** Bowen, Philantha; Duvall Miller, Beth A  
**Cc:** Barnes, Sandy L (CDER); Ripper, Leah W  
**Subject:** RE: NDAs: 22439 & 22442 - Resubmissions - 505b2 Reassessment Inquiry  
**Importance:** High

Philantha,

It appears from your email that the applicant has added a new listed drug relied upon to support this resubmission that was not identified at the time of the original submission. Please confirm that I am not misinterpreting your message.

Unfortunately, this will trigger the MMA provision that will require the applicant to submit a new application. We will discuss this with ORP/OCC on Monday and get back to you ASAP with further instructions. What is the goal date for the RS?

Thanks,  
Kim

---

**From:** Bowen, Philantha  
**Sent:** Thursday, April 22, 2010 9:55 AM  
**To:** Duvall Miller, Beth A  
**Cc:** Quaintance, Kim M  
**Subject:** FW: NDAs: 22439 & 22442 - Resubmissions - 505b2 Reassessment Inquiry

Hello Beth,

I am in the processing of re-evaluating the b2 assessment form for NDAs 22439 and 22442 (Rezira's). It appears that I do need to re-submit the forms to you because the RLD has changed. The sponsor is relying in Hi-Tech Syrup, since Hycodan has been discontinued from marketing.

My apologies. I hope to get this to you by tomorrow, if not before.

In updating the b2 forms, I have a question:

1) Question 6 on b2 form: For resubmissions, is the information cumulative? This implies that I would only need to add the new RLD listed in the resubmission. OR Should I update the form with only the RLD listed (per 356h/cover letter) in the resubmission, as well as RLD included in the resubmitted annotated labeling?

Sincerely,

***Philantha***

---

**From:** Duvall Miller, Beth A  
**Sent:** Tuesday, December 29, 2009 11:05 AM  
**To:** Bowen, Philantha; Quaintance, Kim M  
**Subject:** RE: NDAs: 22439 & 22442 - Resubmissions - 505b2 Reassessment Inquiry

Hi Philantha,

Thanks for the heads-up. If nothing has changed wrt the b(2) information in the application, then there is no need to provide us with another b(2) assessment. Thanks for asking.

We'll get these applications back in our queue and will be in touch shortly before your new PDUFA date. Please let us know if you intend to take an early action. Also note that we do need to clear every b(2) application before each and every action.

Beth

***Beth Duvall-Miller***

Team Leader, Regulatory Affairs Team  
CDER/Office of New Drugs

Direct Phone Number: (301) 796-0513  
OND IO Phone Number: (301) 796-0700  
Fax: (301) 796-9855

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**From:** Bowen, Philantha  
**Sent:** Tuesday, December 29, 2009 10:31 AM  
**To:** Quaintance, Kim M; Duvall Miller, Beth A  
**Subject:** NDAs: 22439 & 22442 - Resubmissions - 505b2 Reassessment Inquiry

Hello,

We have Class 2 resubmissions to the CR action taken on NDAs 22439 and 22442. On the previous cycle, the 505b2 forms were submitted to you for review and cleared.

For the resubmissions, do I need to re-submit or do anything in terms of the 505b2 assessments for these applications on this review cycle?

Sincerely,

*Philantha*

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**Philantha M. Bowen, MPH, BSN, RN**  
**CDR, U.S. Public Health Service**  
**Sr. Regulatory Management Officer**  
Food and Drug Administration  
Center for Drug Evaluation and Research/ODEII  
Division of Pulmonary and Allergy Products  
10903 New Hampshire Ave., Bldg 22, Room 3317  
Silver Spring, MD 20993  
☎ 301-796-2466  
☎ 301-796-9718  
✉ [philantha.bowen.fda.hhs.gov](mailto:philantha.bowen.fda.hhs.gov)

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Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** May 16, 2011

<b>To:</b> Janet DeLeon	<b>From:</b> Philantha Bowen
<b>Company:</b> Cypress Pharmaceuticals	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 913-681-0669	<b>Fax number:</b> 301-796-9718
<b>Phone number:</b> 913-681-0667	<b>Phone number:</b> 301-796-2466

**Subject:** NDAs: 22439 and 22442 Re: FDA Labeling Recommendations IR #2

**Total no. of pages including cover:** 34

**Comments:**

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**Document to be mailed:**       YES                       NO

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**NDA 22439 (Zutripro)**  
**NDA 22442(Rezira)**  
**Cypress Pharmaceuticals, Inc.**

Your submissions dated December 8, 2010, and May 3, 2011, to NDAs 22439 and 22442 are under review and we have a request for labeling revisions. The FDA-proposed insertions are underlined and deletions are in strike-out. These comments are not all-inclusive and we may have additional comments and/or requests as we continue our review of the labels.

Submit revised labeling incorporating the recommended changes shown in the attached marked up Package Inserts by May 19, 2011. Submit a clean copy and a tracked change version of the labels officially to the NDAs. In addition, please forward a courtesy copy to me via email.

If there are any questions, contact Philantha Bowen, Senior Regulatory Management Officer, at 301-796-2466.

*{See appended electronic signature page}*

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Philantha Montgomery Bowen, MPH, RN  
Sr. Regulatory Project Management Officer  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure: (2) Package Inserts

Drafted by: Bowen/May 13, 2011

Clearance: Barnes/May 13, 2011  
Xu/May 13, 2011  
Durmowicz/May 13, 2011  
Shang/May 13, 2011  
Doddapaneni/May 13, 2011  
Lee/May 13, 2011  
Robison/May 13, 2011

Finalized by: Bowen/May 16, 2011

31 Page(s) of Draft Labeling has been  
Withheld in Full as B4 (CCI/TS)  
immediately following this page

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/s/  
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PHILANTHA M BOWEN  
05/16/2011

## Bowen, Philantha

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**From:** Greeley, George  
**nt:** Tuesday, May 03, 2011 3:19 PM  
**J:** Bowen, Philantha  
**Cc:** Suggs, Courtney; Lee, Catherine S.  
**Subject:** NDA's 22-439 Rezira & 22-442 Zutripro

**Importance:** High

**Attachments:** 1\_Pediatric\_Record.pdf; 1\_Peds Page.doc

Hi Philantha,

The email serves as confirmation of the review for Rezira<sup>(b)(4)</sup> (hydrocodone, chlorpheniramine, and pseudoephedrine) and Zutripro (hydrocodone, bitartrate and pseudoephedrine) conducted by the PeRC PREA Subcommittee on May 26, 2010.

The Division presented a partial waiver for patients ages birth to five years and a deferral for patients six to seventeen years for the indications of relief of cough and nasal congestion associated with common cold, relief of symptoms including nasal congestion associated with upper respiratory allergies<sup>(b)(4)</sup>

The PeRC agreed with the Division to grant a partial waiver and deferral for this product. The pediatric record is attached for Rezira<sup>(b)(4)</sup> and pediatric page for Zutripro.



1\_Pediatric\_Record 1\_Peds Page.doc  
.pdf (54 KB)... (413 KB)

Thank you.

George Greeley  
Regulatory Health Project Manager  
Pediatric and Maternal Health Staff  
FDA/CDER/OND  
10903 New Hampshire Avenue  
Bldg. 22, Room 6467  
Silver Spring, MD 20993-0002  
Phone: 301.796.4025  
Email: [george.greeley@fda.hhs.gov](mailto:george.greeley@fda.hhs.gov)

Please consider the environment before printing this e-mail.



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** April 28, 2011

<b>To:</b> Janet DeLeon	<b>From:</b> Philantha Bowen, MPH, RN
<b>Company:</b> Cypress Pharmaceuticals	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 913-681-0669	<b>Fax number:</b> 301-796-9718
<b>Phone number:</b> 913-681-0667	<b>Phone number:</b> 301-796-2466

**Subject:** NDAs: 22439 and 22442 Re: FDA Labeling Recommendations IR

**Total no. of pages including cover:** 35

**Comments:**

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**Document to be mailed:**       YES                       NO

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**NDA 22439 (Zutripro)**  
**NDA 22442(Rezira)**  
**Cypress Pharmaceuticals, Inc.**

We have begun our review of the label in your December 8, 2010, submissions to NDAs 22439 and 22442 and we have a request for labeling revisions. The FDA-proposed insertions are underlined and deletions are in strike-out. Note that we have comments inserted in the label, as appropriate, to clarify our revisions. These comments are not all-inclusive and we may have additional comments and/or requests as we continue our review of the labels.

Submit revised labeling incorporating the changes shown in the attached marked up Package Insert by May 5, 2011. Submit a clean copy and a tracked change version of the label officially to the NDAs. In addition, please forward a courtesy copy to me via email.

*{See appended electronic signature page}*

---

Philantha Montgomery Bowen, MPH, RN  
Sr. Regulatory Project Management Officer  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

32 Page(s) of Draft Labeling has been Withheld  
in Full as B4 (CCI/TS) immediately following  
this page

Drafted by: Bowen/April 22, 2011

Clearance: Barnes/April 27, 2011  
Xu/April 27, 2011  
Durmowicz/April 27, 2011  
Shang/April 26, 2011  
Doddapaneni/April 26, 2011  
Lee/April 25, 2011  
Robison/April 25, 2011  
Gilbert-McClain/April 27, 2011

Finalized by: Bowen/April 28, 2011

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/s/  
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PHILANTHA M BOWEN  
04/28/2011

## **Bowen, Philantha**

---

**From:** Bowen, Philantha  
**Sent:** Thursday, April 14, 2011 11:48 AM  
**To:** 'DeLeon, Janet'  
**Subject:** NDA: 22439 - Zutripro

Hi Janet,

DMEPA has found the tradename Zutripro conditionally acceptable for NDA 22439. Please submit revised carton and container labels reflecting this name for this NDA.

If you have any questions regarding the tradename & this request, contact Nichelle Rashid.

Sincerely,

*Philantha*

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**Philantha M. Bowen, MPH, BSN, RN**  
**CDR, U.S. Public Health Service**  
**Sr. Regulatory Management Officer**

Food and Drug Administration  
Center for Drug Evaluation and Research/ODEII  
Division of Pulmonary, Allergy, and Rheumatology Products  
10905 New Hampshire Ave., Bldg 22, Room 3326  
Silver Spring, MD 20993  
☎ 301-796-2466  
☎ 301-796-9718  
✉ philantha.bowen@fda.hhs.gov

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NDA 022439

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Cypress Pharmaceutical, Inc.  
c/o: Beckloff Associates, Inc.  
Commerce Plaza II, Suite 300  
7400 West 110<sup>th</sup> Street  
Overland Park, KS 66210

ATTENTION: William C. Putnam, Ph.D., R.A.C.  
Director, Executive Consultant  
Scientific Consulting

Dear Dr. Putnam:

Please refer to your New Drug Application (NDA) dated November 6, 2008, received November 7, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hydrocodone Bitartrate, Chlorpheniramine Maleate, and Pseudoephedrine HCl Oral Solution, 5 mg/4 mg/60 mg per 5 mL.

We also refer to your December 10, 2010, correspondence, received December 10, 2010, requesting review of your proposed proprietary name, Zutripro. We have completed our review of the proposed proprietary name, Zutripro and have concluded that it is acceptable.

The proposed proprietary name, Zutripro, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your December 10, 2010, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Philantha Bowen, at (301) 796-2466.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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CAROL A HOLQUIST  
02/24/2011



NDA 22439  
NDA 22442

## INFORMATION REQUEST

Cypress Pharmaceutical, Inc.  
c/o Beckloff Associates, Inc.  
Commerce Plaza II, Suite 300  
7400 West 110<sup>th</sup> Street  
Overland Park, KS 66210

Attention: William Putman, Ph.D., R.A.C.  
Director, Executive Consultant

Dear Dr. Putman:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for hydrocodone/chlorpheniramine/pseudoephedrine and hydrocodone/pseudoephedrine oral solutions.

We also refer to your December 8, 2010, submissions containing a response to our June 11, 2010, complete response letter.

We are reviewing the clinical summary of your submissions and have the following comment and/or information request. We request a prompt written response in order to continue our evaluation of your NDA.

- Clarify if your proposed drug products, for the NDAs listed above, were ever marketed abroad and in the United States as unapproved products. If so, submit safety information and marketing history to both NDA applications.

NDA 22439

NDA 22442

Page 2

If you have any questions, call Philantha Bowen, Regulatory Project Manager, at (301) 796-2466.

Sincerely,

*{See appended electronic signature page}*

Anthony Durmowicz, M.D.  
Clinical Team Leader  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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ANTHONY G DURMOWICZ  
01/31/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): <b>OSE</b>		FROM: Philantha M. Bowen, Project Manager Division of Pulmonary, Allergy, and Rheumatology Drug Products HFD-570		
DATE January 25, 2011	IND NO.	NDA NO. NDA 22439 NDA 22442	TYPE OF DOCUMENT Resubmission	DATE OF DOCUMENT December 8, 2010
NAME OF DRUG Hydrocodone/chlorpheniramine/PSE & Hydrocodone/PSE		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE April 28, 2011
NAME OF FIRM: Cypress Pharmaceuticals				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input checked="" type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
<b>II. BIOMETRICS</b>				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG SAFETY</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
<b>COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:</b>				
<b>RESUBMISSION</b> This is a consult for evaluation and review of the labeling for Hydrocodone/chlorpheniramine/PSE & Hydrocodone/PSE, NDA 22439 and NDA 22442, respectively. This is the third review cycle. The labeling was reviewed during the second cycle. The application received a CR based on failed DSI inspection. The labeling is in electronic format and is located in the EDR in the submission dated December 8, 2010.				
<b>PDUFA Date: June 8, 2011</b>				
SIGNATURE OF REQUESTER		METHOD OF DELIVERY (Check one) X MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

Reference ID: 2896605

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/s/  
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PHILANTHA M BOWEN  
01/25/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR DDMAC LABELING REVIEW CONSULTATION</b> <b>**Please send immediately following the Filing/Planning meeting**</b>	
TO: <b>CDER-DDMAC-RPM</b>		FROM: (Name/Title, Office/Division/Phone number of requestor) Philantha M. Bowen, Project Manager Division of Pulmonary, Allergy, and Rheumatology Drug Products, HFD-570, (Ph) 301-796-2466	
REQUEST DATE January 25, 2011	IND NO.	NDA/BLA NO. NDA 22439 NDA 22442	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
NAME OF DRUG Hydrocodone/chlorpheniramine/PSE & Hydrocodone/PSE	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) April 28, 2011
NAME OF FIRM: Cypress Pharmaceuticals		PDUFA Date: June 8, 2011	
<b>TYPE OF LABEL TO REVIEW</b>			
<b>TYPE OF LABELING:</b> (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE (IFU)		<b>TYPE OF APPLICATION/SUBMISSION</b> <input checked="" type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	
		<b>REASON FOR LABELING CONSULT</b> <input checked="" type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION	
<b>EDR link to submission:</b> The network location is : EDR Location: <a href="\\CDSESUB1\EVSPROD\NDA022439\022439.enx">\\CDSESUB1\EVSPROD\NDA022439\022439.enx</a> EDR Location: <a href="\\CDSESUB1\EVSPROD\NDA022442\022442.enx">\\CDSESUB1\EVSPROD\NDA022442\022442.enx</a>  <b>The submission date: December 8, 2010</b>			
<b>Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.</b>			
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b> <b>RESUBMISSION</b> This is a consult for evaluation and review of the labeling for Hydrocodone/chlorpheniramine/PSE & Hydrocodone/PSE, NDA 22439 and NDA 22442, respectively. This is the third review cycle. The labeling was reviewed during the second cycle. The application received a CR based on failed DSI inspection. The labeling is in electronic format and is located in the EDR in the submission dated December 8, 2010.			
SIGNATURE OF REQUESTER			
SIGNATURE OF RECEIVER		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> eMAIL <input type="checkbox"/> HAND	

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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PHILANTHA M BOWEN  
01/25/2011



NDA 22439

**ACKNOWLEDGE –  
CLASS 2 RESPONSE**

Cypress Pharmaceutical, Inc.  
c/o Beckloff Associates, Inc.  
Commerce Plaza II, Suite 300  
7400 West 110<sup>th</sup> Street  
Overland Park, KS 66210

Attention: William Putman, Ph.D., R.A.C.  
Director, Executive Consultant

Dear Dr. Putman:

We acknowledge receipt on December 8, 2010, of your December 18, 2010, resubmission of your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for hydrocodone, chlorpheniramine, and pseudoephedrine oral solution.

We consider this a complete, class 2 response to our June 11, 2010, action letter. Therefore, the user fee goal date is June 8, 2011.

If you have any questions, call Philantha Bowen, Senior Regulatory Project Management Officer, at (301) 796-2466.

Sincerely,

*{See appended electronic signature page}*

Sandy Barnes  
Chief, Project Management Staff  
Division of Pulmonary, Allergy, and  
Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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PHILANTHA M BOWEN  
12/23/2010  
Acting on Behalf of Sandy Barnes



NDA 022439

**PROPRIETARY NAME REQUEST  
UNACCEPTABLE**

Cypress Pharmaceutical, Inc.  
c/o Beckloff Associates, Inc.  
Commerce Plaza II, Suite 300  
7400 West 110<sup>th</sup> Street  
Overland Park, Kansas 66210

ATTENTION: William C. Putnam, Ph.D., R.A.C.  
Director, Executive Consultant  
Scientific Consulting, Beckloff Associates, Inc.

Dear Dr. Putnam:

Please refer to your New Drug Application (NDA) resubmission dated December 10, 2009, received December 11, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hydrocodone Bitartrate, Chlorpheniramine Maleate, and Pseudoephedrine Hydrochloride Oral Solution, 5 mg/4 mg/60 mg per 5 mL.

We also refer to your April 30, 2010, correspondence, received May 3, 2010, requesting review of your proposed proprietary name, (b) (4). We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons.

(b) (4)

We note that you have proposed an alternate proprietary name in your submission dated May 3, 2010. In order to initiate the review of the alternate proprietary name, (b) (4), a new complete request for proprietary name review must be submitted once you have responded to the deficiencies stated in the Agency's June 11, 2010 Complete Response letter. The review of this alternate name will not be initiated until the new submission is received.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Carolyn Volpe, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5204. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22439

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ORIG-1

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CYPRESS  
PHARMACEUTICA  
L INC

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(b) (4) (HYDROCODONE  
BITARTRATE/CHLORPH

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CAROL A HOLQUIST  
07/27/2010

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 22-439 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Tradename Established/Proper Name: hydrocodone, chlorpheniramine and pseudoephedrine Dosage Form: oral solution		Applicant: Cypress Pharmaceuticals, Inc. Agent for Applicant (if applicable): William Putman, Ph.D., R.A.C. Director, Executive Consultant Beckloff Associates, Inc.
RPM: Philantha Bowen		Division: DPARP
<p><b>NDA:</b> NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><b>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</b> Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)): NDA 5213 Hycodan NDA 19111 Tussionex * NDA 21369 Codeprex * NDA 21082 Tavist Allergy* NDA 21441 Advil Allergy Simus* * 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. Provide a brief explanation of how this product is different from the listed drug.</p> <p>New combination product</p> <p><input type="checkbox"/> If no listed drug, check box and explain:</p> <p><b><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input checked="" type="checkbox"/> No changes    <input type="checkbox"/> Updated    Date of check: May 27, 2010</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p>
❖ Actions		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>June 11, 2010</u></li> </ul>		<input type="checkbox"/> AP <input type="checkbox"/> TA <input checked="" type="checkbox"/> CR

<sup>1</sup> The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

<ul style="list-style-type: none"> <li>Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>	<input type="checkbox"/> None CR 9/18/09
<ul style="list-style-type: none"> <li>If accelerated approval, were promotional materials received? Note: For accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain _____</li> </ul>	<input type="checkbox"/> Received
<ul style="list-style-type: none"> <li>Application Characteristics <sup>2</sup></li> </ul>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority            Chemical classification (new NDAs only): 4</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC         </p> <p>           NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510)  <input type="checkbox"/> Restricted distribution (21 CFR 314.520)            Subpart I <input type="checkbox"/> Approval based on animal studies         </p> <p>           BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41)  <input type="checkbox"/> Restricted distribution (21 CFR 601.42)            Subpart H <input type="checkbox"/> Approval based on animal studies         </p> <p> <input type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC  <input type="checkbox"/> Submitted in response to a Pediatric Written Request         </p> <p>Comments:</p>	
<ul style="list-style-type: none"> <li>BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)</li> </ul>	<input type="checkbox"/> Yes, date
<ul style="list-style-type: none"> <li>BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Public communications (<i>approvals only</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Press Office notified of action (by OEP)</li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<input type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<sup>2</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input checked="" type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes       No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

*If "Yes," skip to question (4) below. If "No," continue with question (2).*

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes       No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

*If "No," continue with question (3).*

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes       No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

*If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes       No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).*

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

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
---	--

**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>3</sup>	9/17/09; 6/11/10
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**Officer/Employee List**

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input type="checkbox"/> Included

**Action Letters**

❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) CR 9/18/09; CR 6/11/10
---	--

**Labeling**

❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	6/8/10
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	11/6/09 Resubmission 12/10/09 Revision 5/17/12
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.  
Version: 5/14/10

<ul style="list-style-type: none"> <li>❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)</li> </ul>	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	5/17/10
<ul style="list-style-type: none"> <li>❖ Proprietary Name           <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> </ul> </li> </ul>	IR 1/6/09 NA 1/11/10 MM 5/4/10 WD 5/7/10 Review 12/29/09
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input checked="" type="checkbox"/> RPM 7/28/09: 6/7/10 <input checked="" type="checkbox"/> DMEPA 5/7/10 <input type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC 5/10/10 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> <li>❖ 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	Filing Review 7/30/09  <input type="checkbox"/> Not a (b)(2) 9/17/09; 4/27/10; 5/27/10; addendum 5/27/10
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP           <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)           <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>5/26/10</u>. PeRC Summary <u>6/8/10</u> If PeRC review not necessary, explain: _____</li> <li>• Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)</li> </ul>	<input checked="" type="checkbox"/> Verified, statement is acceptable

<sup>4</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.  
Version: 5/14/10

❖ Outgoing communications ( <i>letters (except action letters), emails, faxes, telecons</i> )	11/24/08; 1/6/09; 1/16/09; 2/23/09; 4/30/09; 6/3/09; 6/9/09; 12/29/09; 3/26/10; 5/5/10; 5/12/10
❖ Internal memoranda, telecons, etc.	2/29/08; 4/8/09
❖ Minutes of Meetings	
• Regulatory Briefing ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg 6/12/09
• If not the first review cycle, any end-of-review meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> No mtg
• EOP2 meeting ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) ( <i>indicate dates of mtgs</i> )	PreIND 1/14/08
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available ( <i>do not include transcript</i> )	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 9/17/09; 6/11/10
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None See DD Summary Review
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical Information<sup>5</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	See DD Summary Review
• Clinical review(s) ( <i>indicate date for each review</i> )	12/19/08; 7/21/09; 5/26/10
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	Clinical Review 7/21/09, pg 15
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input type="checkbox"/> Not applicable CSS review 9/3/09; 9/11/09; OSE review 8/26/09
❖ Risk Management	
• REMS Documents and Supporting Statement ( <i>indicate date(s) of submission(s)</i> )	
• REMS Memo(s) and letter(s) ( <i>indicate date(s)</i> )	
• Risk management review(s) and recommendations (including those by OSE and CSS) ( <i>indicate date of each review and indicate location/date if incorporated into another review</i> )	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input checked="" type="checkbox"/> None requested

<sup>5</sup> Filing reviews should be filed with the discipline reviews.  
Version: 5/14/10

<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
<b>Biostatistics</b> <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 1/9/09; 7/20/09; 4/30/10; 5/25/10
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input type="checkbox"/> None 5/5/10; 5/20/10
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> None 6/22/09; 5/11/10
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 6/17/09; 5/3/10
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None 7/14/10
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	<input type="checkbox"/> None 12/11/08; 7/8/09; 8/31/09; 4/21/10
❖ Microbiology Reviews	<input type="checkbox"/> Not needed 3/16/09
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) (indicate date of each review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input type="checkbox"/> None P/T 5/20/09; 5/26/09; 5/27/09; 2/22/10

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	7/8/09
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) ( <i>date completed must be within 2 years of action date</i> )	Date completed: 8/31/09 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<input type="checkbox"/> BLAs: TB-EER ( <i>date of most recent TB-EER must be within 30 days of action date</i> )	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation ( <i>check box only, do not include documents</i> )	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed

## Appendix to Action Package Checklist

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

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a 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) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

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

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

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

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

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

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

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

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22439

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ORIG-1

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CYPRESS  
PHARMACEUTICA  
L INC

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(b) (4) (HYDROCODONE  
BITARTRATE/CHLORPH

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/s/  
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CAROL F HILL  
06/10/2010



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II  
Division of Pulmonary and Allergy Products**

**Memorandum of Facsimile Correspondence**

Date: May 12, 2010

To: Janet DeLeon

Company: Hawthorn Pharmaceuticals for Cypress Pharmaceuticals Inc.

Fax: 913-681-0669

Email: [jdelon@cypressrx.com](mailto:jdelon@cypressrx.com)

Phone: 913-681-0667

From: Carol Hill, MS  
Regulatory Health Project Manager  
Division of Pulmonary, Allergy and Rheumatology Products

Subject: Labeling Revisions and Comments II re: NDA 22-439 & NDA 22-442

# of Pages: 10

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Thank you.  
[carol.hill@fda.hhs.gov](mailto:carol.hill@fda.hhs.gov)

NDA 22-439

NDA 22-442

Cypress Pharmaceutical Inc

Please submit revised draft labeling incorporating the attached labeling comments. Be advised that additional labeling comments may be forthcoming as we continue to review the labeling. Note that word changes in sentences may have been italicized for reference but the appropriate font is to be maintained in the labeling. We have also included the labeling comments faxed to you following our May 10, 2010, teleconference. Unless otherwise stated, the comments pertain to the labeling for both NDAs. Submit revised labeling by close of business Monday, May 17, 2010

If you have any questions, contact Carol Hill, Regulatory Health Project Manager at 301-796-1226.

Updated Labeling Comments Package Insert  
May 10, 2010  
NDA 22-439 and NDA 22-442

Unless indicated, these comments apply to both NDA 22-439 and 22-442

1. Section 4 CONTRAINDICATIONS

Insert “inactive” in the sentence in the first bullet

Patients with known hypersensitivity to hydrocodone..... or any of the inactive ingredients of .....

2. Section 5.1 Respiratory Depression (NDA 022-439 only)

Delete the extra sentence: “Exercise caution when administering (b) (4) Oral Solution because of the potential for respiratory depression.”

3. Section 6 ADVERSE REACTIONS

Delete the words (b) (4) from the chlorpheniramine statement  
| “Use of chlorpheniramine, an antihistamine, may result in (b) (4):

4. Section 8.1 Pregnancy (NDA 022-439 only)

Change (Trade name) to TRADENAME in the first sentence

5. Section 8.4 Pediatric Use

Delete the statement: (b) (4)

Revise the statement as follows;  
“The use of hydrocodone bitartrate in children less than 6 years of age has been associated with fatal respiratory depression [see Warnings and Precautions (5.1)]

6. Section 8.5 Geriatric Use

Revise the section as follows:  
Clinical studies have not been conducted with xxxxx Oral Solution. Other reported clinical experience with the individual active ingredients of xxxxxx Oral Solution has not identified differences in responses between the elderly and patients younger than 65 years of age. In general, dose selection for an elderly patient should be cautions, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. The pseudoephedrine contained in xxxx Oral Solution is known to be substantially excreted by the kidney and the risk of toxic reactions to this drug may be greater in patents with impaired renal function. Because elderly patients are more likely to have decreased renal

function, care should be taken in dose selection, and it may be useful to monitor renal function.

#### 7. Section 12.3 Pharmacokinetics

Change (b) (4) to “Specific” in the subheading “(b) (4) Populations”

#### 8. Section 14 CLINICAL STUDIES

Change the statements to read:

Efficacy studies were not conducted with xxx Oral Solution. Efficacy of xxxx Oral Solution is based on demonstration of bioequivalence to the individual reference products  
[See *Pharmacokinetics 12.3*]

Labeling comments NDA 22-439 and 22-442  
May 12<sup>th</sup>, 2010

The following comments pertain to the Package Insert

1. Section 5.2 Drug Dependence

- Delete the statement [redacted] (b) (4)

2. Section 5.3 Head Injury and Increased Intracranial pressure

- Change [redacted] (b) (4) to “effects” in the first sentence to read as follows: The respiratory depression *effects* of opioids and their.....

3. Section 5.4 Activities Requiring Mental Alertness

- Change the sentence [redacted] (b) (4)

to the following statement:

“Advise patients to avoid engaging in hazardous tasks requiring mental alertness and motor coordination after ingestion of xxxx Oral Solution.”

- Change [redacted] (b) (4) to “tasks” in the corresponding fourth bullet under Warnings and Precautions in the Highlights section

4. Section 5.5 Acute Abdominal Conditions

- Delete the phrase [redacted] (b) (4) from the first sentence. The sentence should read as follows:  
“xxxx Oral Solution should be used with caution in patients with acute abdominal conditions since the administration of hydrocodone bitartrate may obscure the diagnosis or .....conditions.”

5. Section 5.8 Cardiovascular and Central Nervous System Effects

- Delete the phrase [redacted] (b) (4) from the first sentence  
“The pseudoephedrine hydrochloride contained in xxxxx.....”

6. [redacted] (b) (4)

(b) (4)

7.

(b) (4)

(b) (4)

#### 8. Section 8.1 Pregnancy

- Insert the following words “of codeine” and “of hydrocodone” so that the paragraph reads as follows:

“Hydrocodone

(b) (4)

#### 9. Section 12.1 Mechanism of Action

Delete the phrase (b) (4) from the sentence in the first paragraph that reads “In excessive doses, hydrocodone (b) (4) will depress respiration. Revise the sentence to read: “In excessive doses, hydrocodone will depress respiration.”

#### 10. Section 13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

- Insert the following words “of hydrocodone” so that the paragraph reads as follows:

“Hydrocodone

Carcinogenicity studies were conducted with codeine, an opiate related to hydrocodone. In 2 year studies in F344/N rats and B6C3F1 mice, codeine showed no evidence of tumorigenicity at dietary doses up to 70 and 400 mg/kg/day, respectively (approximately 30 and 80 times, respectively, the MRHDD of hydrocodone on a mg/m<sup>2</sup> basis).”

11.

(b) (4)

(b) (4)

## 12. Section 17 patient Counseling Information

- Add the following additional safety information and update the Highlights section accordingly:

### 17.4 Activities requiring Mental Alertness

Patients should be advised to avoid engaging in hazardous tasks that require mental alertness and motor coordination such as operating machinery or driving a motor vehicle as xxxx Oral Solution may produce marked drowsiness. *[See Warnings and Precautions (5.4)]*

### 17.5 Drug Dependence

Patients should be cautioned that xxxx Oral Solution contains hydrocodone and can produce drug dependence *[See Warnings and Precautions (5.2)]*

### 17.6 Monoamine Oxidase (MAO) Inhibitors

Patients should be informed that due to its pseudoephedrine component, they should not use xxxx Oral Solution with a monoamine oxidase (MAO) inhibitor or within 14 days of stopping use of an MAO inhibitor. *[See Warnings and Precautions (5.7)]*

The following comments pertain to the Container labels ( (b) (4) and 480 mL)

1. As currently presented, the (b) (4) between Rezira and (b) (4) (TRADENAME) 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 (b) (4) for Rezira and (b) (4) (TRADENAME)

(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.

3. 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.

4. Delete following statement on the side panel of the 480 mL container label:

[Redacted] (b) (4)

The following comments pertain to the container labeling for NDA 22-439

1. As currently presented, the product strength (5 mg/4 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.

2. The contents statement is confusing [Redacted] (b) (4)  
[Redacted] (see below).

[Redacted] (b) (4)

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

**Contains:**

Hydrocodone  
Bitartrate.....5 mg/5 mL

**Warning: May be habit forming.**

Chlorpheniramine  
Maleate.....4 mg/5 mL

Pseudoephedrine  
Hydrochloride.....60 mg/5 mL

The following comments pertain to the container labeling for NDA 22-442

1. 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.

2. The contents statement is confusing [redacted] (b) (4)  
[redacted] (see below).

[redacted] (b) (4)

Since practitioners can calculate the amount [redacted] (b) (4) and in order to avoid confusion, we recommend deleting the [redacted] (b) (4) since the concentration of the product is per 5 mL. Revise the [redacted] (b) (4) column to delete [redacted] (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

The following comments pertain to the Carton labeling ([redacted] (b) (4) sample, 12 count)

1. Refer to the container comments 1 and 2 for NDA 22-439 and 22-442
2. The thin white font [redacted] (b) (4) 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.

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/

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CAROL F HILL  
05/12/2010



NDA 022439

**PROPRIETARY NAME REQUEST  
WITHDRAWN**

Cypress Pharmaceuticals, Inc.  
c/o Beckloff Associates, Inc.  
Commerce Plaza II, Suite 300  
7400 West 110<sup>th</sup> Street  
Overland Park, Kansas 66210

ATTENTION: William C. Putnam, Ph.D., R.A.C.  
Director, Executive Consultant  
Scientific Consulting, Beckloff Associates, Inc.

Dear Dr. Putnam:

Please refer to your New Drug Application (NDA) resubmission dated December 10, 2009, received December 11, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hydrocodone Bitartrate, Chlorpheniramine Maleate, and Pseudoephedrine Hydrochloride Oral Solution, 5 mg/4 mg/60 mg per 5 mL.

We acknowledge receipt of your April 27, 2010 correspondence, on April 28, 2010, notifying us that you are withdrawing your February 17, 2010 request for a review of the proposed proprietary name (b) (4). This proposed proprietary name request is considered withdrawn as of April 28, 2010.

If you intend to have a proprietary name for this product, a new request for a proposed proprietary name review should be submitted.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Carolyn Volpe, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5204. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Philantha Bowen at 301-796-2466.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22439

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ORIG-1

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CYPRESS  
PHARMACEUTICA  
L INC

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(b) (4) (HYDROCODONE  
BITARTRATE/CHLORPH

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CAROL A HOLQUIST  
05/07/2010



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II  
Division of Pulmonary and Allergy Products**

## **Memorandum of Facsimile Correspondence**

Date: May 5, 2010

To: William C. Putnam, Ph.D., R.A.C.

Company: Beckloff Associates for Cypress Pharmaceuticals Inc.

Fax: 913-451-3846

Phone: 913-661-3826

From: Carol Hill, MS  
Regulatory Health Project Manager  
Division of Pulmonary, Allergy and Rheumatology Products

Subject: Labeling Revisions and Comments re: NDA 22-439 & NDA 22-442

# of Pages: 43

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Thank you.

[carol.hill@fda.hhs.gov](mailto:carol.hill@fda.hhs.gov)

**Please confirm receipt.**

NDA 22-439

NDA 22-442

Cypress Pharmaceutical Inc.

The FDA proposed recommended revisions to the package insert for Tradename (hydrocodone bitartrate, chlorpheniramine maleate, and pseudoephedrine hydrochloride) Oral Solution (NDA 22-439) and REZIRA (hydrocodone bitartrate, and pseudoephedrine hydrochloride) Oral Solution (NDA 22-442) have been made using the clean copies of the Word version of the package insert submitted on December 10, 2009 FDA-proposed insertions are underlined and deletions are in strike-out. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as the label is continued to be reviewed. Where appropriate, our rationale for the proposed labeling changes is provided as "FDA comments" throughout the label. Please submit revised labeling incorporating the Division's labeling changes no later than close of business Thursday May 13<sup>th</sup>, 2010.

We have the following general comment.

Do not use all capital letters in the cross-references embedded in the text in the FPI; use italics for cross-references.

If you have any questions, contact Carol Hill, Regulatory Health Project Manager at 301-796-1226.

40 Page(s) of Draft Labeling has been Withheld in Full as B4  
(CCI/TS) immediately following this page

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/

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CAROL F HILL  
05/05/2010



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Advice  
**Meeting Category:** Teleconference

**Meeting Date and Time:** April 21, 2010, 2:30-3:00 pm  
**Meeting Location:** White Oak Building 22, Room 3201

**Application Number:** NDA 022439  
**Proposed Proprietary Name:** (b) (4)  
**Proposed Indication:** Relief of cough; Relief of nasal congestion  
**Sponsor/Applicant Name:** Cypress Pharmaceuticals, Inc.

**Meeting Chair:** Felicia Duffy  
**Meeting Recorder:** Carolyn Volpe

**FDA ATTENDEES**

Office of Surveillance and Epidemiology

Felicia Duffy Safety Evaluator, Division of Medical Error Prevention and Analysis  
Zachary Oleszczuk Safety Evaluator, Division of Medical Error Prevention and Analysis  
Carol Holoquist Director, Division of Medical Error Prevention and Analysis  
Carolyn Volpe Safety Regulatory Project Manager

Division of Pulmonary, Allergy, and Rheumatology Products

Philantha Bowen Regulatory Project Manager  
Xu Wang Medical Officer  
Sally Seymour Deputy Director of Safety

**SPONSOR ATTENDEES**

Cypress Pharmaceuticals, Inc.

Rob Lewis Chief Scientific Officer  
Janet K. DeLeon Director of Product Development  
William (Trey) Putnam Director, Executive Consultant, Scientific Consulting,, Beckloff Associates

**BACKGROUND:**

Cypress Pharmaceuticals requested review of (b) (4) as proposed proprietary names for NDA 022439. (b) (4) is the second proposed name for this application, and (b) (4) is the third proposed name for this application. The Division of Medical Error Prevention and Analysis (DMEPA) found the primary name, (b) (4) unacceptable (b) (4). DMEPA has evaluated the proposed proprietary names, (b) (4), and found both names unacceptable.

Cyprees Pharmaceuticals also has a second pending NDA under review at the FDA. The proprietary name, Rezira, has been reviewed by DMEPA and was found acceptable for this NDA.

**MEETING OBJECTIVES:**

- Discuss DMEPA's objection to the proposed proprietary names
- Discuss the issues identified with the proposed names
- Request a new proprietary name submission

**DISCUSSION POINTS:**

- FDA conveyed to Cypress their review findings for the proposed proprietary names, (b) (4). FDA finds (b) (4) unacceptable (b) (4).
- FDA conveyed to Cypress the proposed proprietary name, (b) (4) is unacceptable (b) (4).
- FDA conveyed to Cypress that the review for these names could be finalized and an unacceptable letter would be issued, or Cypress could withdraw (b) (4) and submit an alternative proprietary name for review. Cypress acknowledged these options, and inquired if there would be a difference in review time. FDA responded by letting Cypress know any proprietary name review will require 90 days, but withdrawing and submitting a new proprietary name would allow DMEPA to begin their review sooner.

**DECISIONS (AGREEMENTS) REACHED:**

The Sponsor agreed to withdraw the name, (b) (4), and submit a new proprietary name for review by DMEPA.

**ACTION ITEMS:**

- None

**ATTACHMENTS AND HANDOUTS:**

- None

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22439

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ORIG-1

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CYPRESS  
PHARMACEUTICA  
L INC

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(b) (4) (HYDROCODONE  
BITARTRATE/CHLORPH

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CAROLYN A VOLPE  
05/04/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): <b>Controlled Substance Staff</b>		FROM: Philantha M. Bowen, Project Manager Division of Pulmonary and Allergy Drug Products ,HFD-570		
DATE March 29, 2010	IND NO.	NDA NO. 22-439, 22-442	TYPE OF DOCUMENT N	DATE OF DOCUMENT December 10, 2009
NAME OF DRUG (b) (4), Rezira,		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE April 13, 2010
NAME OF FIRM: Cypress Pharmaceuticals				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
<b>II. BIOMETRICS</b>				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG SAFETY</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
<b>COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:</b>  This is a consult request for your attendance and input at the mid-cycle/wrap meeting on April 13, 2010, for NDAs 22439 and 22442.  We acknowledge the CSS recommendations provided for these products during the first review cycle. Cypress has submitted a complete response dated December 10, 2010. The documents for these applications are electronic and located in the EDR.  (N-22-439 and N-22-442) ; PDUFA Date: June 11, 2010				
SIGNATURE OF REQUESTER		METHOD OF DELIVERY (Check one) X MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/

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PHILANTHA M BOWEN  
03/30/2010



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** March 26, 2010

<b>To:</b> Dr. William C. Putnam	<b>From:</b> Philantha Bowen
<b>Company:</b> Beckloff Associates, Inc. for Cypress Pharmaceutical	Division of Pulmonary and Allergy Drug Products
<b>Fax number:</b> 913-451-3846	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 913-451-3955	<b>Phone number:</b> 301-796-2466

**Subject:** CMC information request for NDA 22-439 & NDA 22-442

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**Total no. of pages including  
cover:** 2

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**Comments:** Please Confirm Receipt

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**Document to be mailed:**                      YES                      x NO

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THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 22439  
NDA 22442  
Cypress Pharmaceutical, Inc.

Your submissions dated December 10, 2009, to NDAs 22-439 and NDA 22-442, are currently under review. We have the following request for information:

Include a second standard solution in method SOP-QC-375 as a control standard and revise the method to include relevant calculations.

Submit your responses to me via telephone facsimile to 301-796-9728 or email at [Philantha.Bowen@fda.hhs.gov](mailto:Philantha.Bowen@fda.hhs.gov). Your response will subsequently need to be submitted officially to the NDAs. If you have any questions, please contact Philantha Bowen, Regulatory Project Manager, at 301-796-2466.

Drafted by: Shen/March 25, 2010

Initialed by: Barnes/March 26, 2010  
Peri/March 25, 2010  
Schroeder/March 25, 2010

Finalized by: Bowen/March 26, 2010

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/

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PHILANTHA M BOWEN  
03/26/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			<b>REQUEST FOR CONSULTATION</b>	
TO ( <i>Division/Office</i> ): <b>PharmTox Review Team (Dr. Jean Wu)</b>			FROM: <b>Xiaobin Shen, Ph.D.</b> CMC Reviewer, DPAP in ONDQA/DPA1/Branch 2	
DATE: <b>Dec. 17, 2009</b>	NDA: <b>22439</b>	TYPE OF DOCUMENT: <b>NDA</b>	DATE OF DOCUMENT <b>10-Dec-2009</b>	
NAME OF DRUG (b) (4)	PRIORITY CONSIDERATION: <b>S</b>	CLASSIFICATION OF DRUG: <b>3</b>	DESIRED COMPLETION DATE: <b>Jan. 31, 2010</b>	
NAME OF FIRM: <b>Cypress Pharmaceuticals, Inc.</b>				
<b>REASON FOR REQUEST:</b> (b) (4) of chlorpheniramine maleate manufactured based on DMF (b) (4) is a potential structural alert. The agency requested the holder to complete genotoxicity study. The study results have been submitted to DMF (b) (4) vol. B5.1. Please evaluate if the study results support the specification of (b) (4) level in the drug substance.				
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b>  Additional information that may help your review —  (b) (4) It has the structure below.  (b) (4)          The previous pharmtox review performed by Dr. Jean Wu is embedded below. I currently have DMF (b) (4) vol. B5.1, please let me know when you need it.  Thanks!  Xiaobin.				



Application Type/Number	Submission Type/Number	Submitter Name	Product Name
(b) (4)	ORIG-1	(b) (4)	CHLORPHENIRAMINE MALEATE USP
NDA-22439	ORIG-1	CYPRESS PHARMACEUTICA L INC	(b) (4) (HYDROCODONE BITARTRATE/CHLORPH

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/s/

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XIAOBIN SHEN  
02/22/2010  
Consult request.

PRASAD PERI  
02/22/2010  
I concur



NDA 022439

**PROPRIETARY NAME REQUEST  
UNACCEPTABLE**

Cypress Pharmaceutical, Inc.  
c/o Beckloff Associates, Inc.  
Commerce Plaza II, Suite 300  
7400 West 110th Street  
Overland Park, KS 66210

ATTENTION: William C. Putnam, Ph.D., R.A.C.  
Director, Executive Consultant,  
Scientific Consulting, Beckloff Associates, Inc.

Dear Dr. Putnam:

Please refer to your New Drug Application (NDA) resubmission dated December 10, 2009, received December 11, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hydrocodone Bitartrate, Chlorpheniramine Maleate, and Pseudoephedrine Hydrochloride Oral Solution, 5 mg/4 mg/60 mg per 5 mL.

We also refer to your January 26, 2009, correspondence, received January 27, 2009, requesting review of your proposed proprietary name, (b) (4). We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable (b) (4)

(b) (4)

(b) (4)

If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the draft Guidance for Industry, Complete Submission for the Evaluation of Proprietary Names, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”).

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Carolyn Volpe, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5204. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Philantha Bowen at (301) 796-2466.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22439

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ORIG-1

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CYPRESS  
PHARMACEUTICA  
L INC

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(b) (4) (HYDROCODONE  
BITARTRATE/CHLORPH

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/s/  
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CAROL A HOLQUIST  
01/11/2010



NDA 22439

**ACKNOWLEDGE CLASS 2 RESPONSE**

Cypress Pharmaceutical, Inc.  
c/o Beckloff Associates, Inc.  
Commerce Plaza II, Suite 300  
7400 West 110<sup>th</sup> Street  
Overland Park, KS 66210

Attention: William Putman, Ph.D., R.A.C.  
Director, Executive Consultant

Dear Dr. Putman:

We acknowledge receipt on December 11, 2009, of your December 10, 2009, resubmission to your new drug application for (b) (4) (hydrocodone, chlorpheniramine, and pseudoephedrine) Oral Solution.

We consider this a complete, class 2 response to our September 18, 2009, action letter. Therefore, the user fee goal date is June 11, 2010.

If you have any questions, call Philantha Bowen, Senior Regulatory Management Officer, at (301) 796-2466.

Sincerely,

*{See appended electronic signature page}*

Sandy Barnes  
Chief, Project Management Staff  
Division of Pulmonary and Allergy Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22439

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ORIG-1

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CYPRESS  
PHARMACEUTICA  
L INC

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(b) (4) (HYDROCODONE  
BITARTRATE/CHLORPH

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PHILANTHA M BOWEN

12/29/2009

Acting on Behalf of Sandy Barnes

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): <b>Division of Drug, Marketing, Advertising and Communication (DDMAC), HFD-42 PKLN Rm. 17B-17</b>		FROM: Philantha M. Bowen, Project Manager Division of Pulmonary and Allergy Drug Products, HFD-570		
DATE December 23, 2009	IND NO.	NDA NO. 22-439	TYPE OF DOCUMENT Resubmission	DATE OF DOCUMENT December 11, 2009
NAME OF DRUG (b) (4)	PRIORITY CONSIDERATION Standard		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE April 16, 2009
NAME OF FIRM: <b>Cypress Pharmaceuticals</b>				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Labeling Review				
<b>II. BIOMETRICS</b>				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG SAFETY</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:				
<b>RESUBMISSION</b> This is a request for an evaluation and review of the labeling for NDA 22-439 (b) (4) Oral Solution. The labeling is in electronic format and is located in the EDR in the submission dated December 11, 2009. We have also submitted consults for other related NDA: 22-442.				
<b>PDUFA DATE: June 11, 2010</b>				
SIGNATURE OF REQUESTER		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22439

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ORIG-1

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CYPRESS  
PHARMACEUTICA  
L INC

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(b) (4) (HYDROCODONE  
BITARTRATE/CHLORPH

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PHILANTHA M BOWEN  
12/23/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): <b>OSE</b>		FROM: Philantha M. Bowen, Project Manager Division of Pulmonary and Allergy Drug Products ,HFD-570		
DATE December 23, 2009	IND NO.	NDA NO. 22-439	TYPE OF DOCUMENT Resubmission	DATE OF DOCUMENT December 10, 2009
NAME OF DRUG (b) (4)	PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE April 16, 2010	
NAME OF FIRM: <b>Cypress Pharmaceuticals</b>				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
<b>II. BIOMETRICS</b>				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG SAFETY</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:				
<b>RESUBMISSION</b> This is a consult for a labeling review of (b) (4) The Package insert is electronic and located in the EDR in the submission dated December 11, 2009. We have also submitted consults for the other related NDAs: N 22-442  <b>PDUFA DATE: June 11, 2010</b>				
SIGNATURE OF REQUESTER		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22439

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ORIG-1

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CYPRESS  
PHARMACEUTICA  
L INC

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(b) (4) (HYDROCODONE  
BITARTRATE/CHLORPH

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PHILANTHA M BOWEN  
12/23/2009

## ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 22-439 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: (b) (4) Established/Proper Name: hydrocodone, chlorpheniramine, and pseudoephedrine Dosage Form: oral solution		Applicant: Cypress Pharmaceuticals, Inc. Agent for Applicant (if applicable): William Putman, Ph.D., R.A.C. Director, Executive Consultant Beckloff Associates, Inc.
RPM: Philantha Bowen		Division: Division of Pulmonary and Allergy Products
<p><b>NDA:</b> NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p><b>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</b> Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p><i>NDA 5213 Hycodan</i> <i>NDA 19111 Tussionex *</i> <i>NDA 21369 Codeprex *</i> <i>NDA 21082 Tavist Allergy*</i> <i>NDA 21441 Advil Allergy Simus*</i></p> <p><i>* 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.</i></p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><i>New combination product</i></p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p><b>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</b></p> <p><input checked="" type="checkbox"/> No changes      <input type="checkbox"/> Updated</p> <p>Date of check: <i>August 16, 2009</i></p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p> <p><b>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</b></p>

<sup>1</sup> The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ User Fee Goal Date Action Goal Date (if different)	User fee: September 7, 2009 Action: September 17, 2009
❖ Actions	
<ul style="list-style-type: none"> <li>• Proposed action</li> </ul>	<input type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input checked="" type="checkbox"/> CR
<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>	<input checked="" type="checkbox"/> None
❖ Promotional Materials ( <i>accelerated approvals only</i> ) Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance <a href="http://www.fda.gov/cder/guidance/2197dft.pdf">www.fda.gov/cder/guidance/2197dft.pdf</a> ). If not submitted, explain _____	<input type="checkbox"/> Received

❖ Application <sup>2</sup> Characteristics		
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 4		
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan drug designation		
<input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Direct-to-OTC		
NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies		BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies
<input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC		
Comments: _____		
❖ Date reviewed by PeRC ( <i>required for approvals only</i> ) If PeRC review not necessary, explain: <i>CR action</i>		July 29, 2009
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM ( <i>approvals only</i> )		<input type="checkbox"/> Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )		<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )		
• Office of Executive Programs (OEP) liaison has been notified of action		<input type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)		<input type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated		<input type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<sup>2</sup> All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input checked="" type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes       No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

*If "Yes," skip to question (4) below. If "No," continue with question (2).*

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes       No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

*If "No," continue with question (3).*

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes       No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

*If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes       No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).*

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

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes    <input type="checkbox"/> No</p>
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**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>3</sup>	
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**Officer/Employee List**

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input type="checkbox"/> Included

**Action Letters**

❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) CR: September 17, 2009
---	---

**Labeling**

❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	none
<ul style="list-style-type: none"> <li>• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	none
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	November 6, 2008
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	
❖ Medication Guide/Patient Package Insert/Instructions for Use ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> None

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.  
Version: 9/5/08

<ul style="list-style-type: none"> <li>• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date at upper right of first page of each submission</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most-recent division proposal for (only if generated after latest applicant submission)</li> </ul>	None
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling</li> </ul>	Original sub date: 11/6/08
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input checked="" type="checkbox"/> RPM 7/28/09 <input type="checkbox"/> DMEDP <input type="checkbox"/> DRISK <input type="checkbox"/> DDMAC <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews Clin Pharm 7/20/09
<ul style="list-style-type: none"> <li>❖ Proprietary Name                         <ul style="list-style-type: none"> <li>• Review(s) (<i>indicate date(s)</i>)</li> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> </ul> </li> </ul>	Under review
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> </ul>	7/30/09
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input type="checkbox"/> Included (N/A: CR Action)
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ora/compliance_ref/aip_page.html">www.fda.gov/ora/compliance_ref/aip_page.html</a></li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant in on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP                         <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)</li> </ul>	<input checked="" type="checkbox"/> Verified, statement is acceptable
<ul style="list-style-type: none"> <li>❖ Postmarketing Requirement (PMR) Studies</li> </ul>	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Outgoing communications (<i>if located elsewhere in package, state where located</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Incoming submissions/communications</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Postmarketing Commitment (PMC) Studies</li> </ul>	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Outgoing Agency request for postmarketing commitments (<i>if located elsewhere in package, state where located</i>)</li> </ul>	

<sup>4</sup> Filing reviews for other disciplines should be filed behind the discipline tab.

<ul style="list-style-type: none"> <li>Incoming submission documenting commitment</li> </ul>	
❖ Outgoing communications ( <i>letters (except previous action letters), emails, faxes, telecons</i> )	11/24/08; 1/6/09; 1/16/09; 2/23/09; 4/30/09; 6/3/09; 6/9/09
❖ Internal memoranda, telecons, etc.	2/29/08; 4/8/09
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>PeRC (<i>indicate date; approvals only</i>)</li> </ul>	<input checked="" type="checkbox"/> Not applicable
<ul style="list-style-type: none"> <li>Pre-Approval Safety Conference (<i>indicate date; approvals only</i>)</li> </ul>	<input checked="" type="checkbox"/> Not applicable
<ul style="list-style-type: none"> <li>Regulatory Briefing (<i>indicate date</i>)</li> </ul>	<input type="checkbox"/> No mtg June 12, 2009
<ul style="list-style-type: none"> <li>Pre-NDA/BLA meeting (<i>indicate date</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>EOP2 meeting (<i>indicate date</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>Other (e.g., EOP2a, CMC pilot programs)</li> </ul>	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>Date(s) of Meeting(s)</li> </ul>	
<ul style="list-style-type: none"> <li>48-hour alert or minutes, if available</li> </ul>	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 9/17/09
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None see DD memo
<b>Clinical Information<sup>5</sup></b>	
❖ Clinical Reviews	
<ul style="list-style-type: none"> <li>Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>	See DD Memo
<ul style="list-style-type: none"> <li>Clinical review(s) (<i>indicate date for each review</i>)</li> </ul>	12/19/08; 7/21/09
<ul style="list-style-type: none"> <li>Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
❖ Safety update review(s) ( <i>indicate location/date if incorporated into another review</i> )	
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	Clinical review 7/21/09, pg 15
❖ Clinical reviews from other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	CSS review 9/3/09; OSE review 8/26/09
❖ Risk Management <ul style="list-style-type: none"> <li>Review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> <li>REMS Memo (<i>indicate date</i>)</li> <li>REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> </ul>	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input checked="" type="checkbox"/> None requested
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None

<sup>5</sup> Filing reviews should be filed with the discipline reviews.  
Version: 9/5/08

Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
<b>Biostatistics</b> <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Statistical Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None <i>See concurrence on primary reviews</i>
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 1/9/09; 7/20/09
❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of DSI letters)</i>	<input checked="" type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 6/22/09
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 6/17/09
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None
❖ DSI Nonclinical Inspection Review Summary <i>(include copies of DSI letters)</i>	<input checked="" type="checkbox"/> None requested
<b>CMC/Quality</b> <input type="checkbox"/> None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 7/14/09
• CMC/product quality review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 12/11/08; 7/8/09; 8/31/09
• BLAs only: Facility information review(s) <i>(indicate dates)</i>	<input checked="" type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) <i>(indicate date of each review)</i>	3/16/09 <input type="checkbox"/> Not needed
• BLAs: Sterility assurance, product quality microbiology <i>(indicate date of each review)</i>	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input type="checkbox"/> None Pharm/tox: 5/20/09; 5/26/09
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	7/8/09
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	

<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed
❖ Facilities Review/Inspection	
<ul style="list-style-type: none"> <li>• NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>)</li> </ul>	Date completed: 8/31/09 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<ul style="list-style-type: none"> <li>• BLAs: <ul style="list-style-type: none"> <li>○ TBP-EER</li> <li>○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) (<i>date completed must be within 60 days prior to AP</i>)</li> </ul> </li> </ul>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation Date completed: <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold

## Appendix A to Action Package Checklist

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

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a 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) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

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

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

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

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

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

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

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

Drafted by: Bowen/August 16, 2009  
Revised by:  
Initialed by:  
Finalized by:

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

PHILANTHA M BOWEN  
09/17/2009



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** June 9, 2009

<b>To:</b> Dr. William Putnam, R.A.C.	<b>From:</b> Philantha Bowen, MPH, RN
<b>Company:</b> Cypress Pharmaceuticals c/o Beckloff Associates, Inc.	Division of Pulmonary and Allergy Drug Products
<b>Fax number:</b> 913-451-3846	<b>Fax number:</b> 301-796-9718
<b>Phone number:</b> 913-451-3955	<b>Phone number:</b> 301-796-2466
<b>Subject:</b> NDAs 22-439; 22-442 [REDACTED]	(b) (4)

---

**Total no. of pages including cover:** 5      **RE:** Clinical Pharmacology Updates for Hydrocodone Combination Products

---

**Comments:**

---

**Document to be mailed:**       YES       NO

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NDA 22-439 – (b) (4)  
NDA 22-442 – Rezira

(b) (4)  
Cypress Pharmaceuticals, Inc.

We have reviewed your submissions dated March 4, 2009, to the above listed NDAs. We have the following general comments and/or recommendations in response to the questions (below in italics) contained in each of the submissions.

GENERAL COMMENTS:

The Office of Clinical Pharmacology (OCP) is providing sponsors with general guidelines regarding the types of clinical pharmacology information that are needed in the development program of combination products containing hydrocodone.

The following information should be included in the submission to the Agency; (1) Relative bioavailability/bioequivalence (BA/BE) results of each ingredient in your fixed dose combination product to those in the reference products, (2) Drug-drug interaction potential among the ingredients of the proposed fixed dose combination product, (3) Formulation effect on each ingredient of the proposed fixed dose combination product; and (4) Food effect on the proposed fixed dose combination. In addition, for an extended release product, steady-state PK information of the combination product (e.g.,  $AUC_{0-\tau}$ ,  $C_{max_{ss}}$ , and  $C_{min_{ss}}$ ) and an alcohol interaction study are needed. Alcohol interaction study can be an *in vitro* study and if the *in vitro* study shows an interaction potential, an *in vivo* study should be conducted.

There are many approaches that can be pursued to gather this information but the following approach is deemed acceptable by the OCP:

For simple solutions, which do not contain (b) (4) any excipients known to affect the bioavailability of the drug (i.e., AUC and  $C_{max}$ ), the bioequivalence (BE) study should compare the proposed combination product to each of the individual components. This BE study should be designed to meet the BE criteria of 90% confidence interval of geometric mean ratio of  $C_{max}$  and AUC being contained within 80 and 125%. If this BE study is conducted as mentioned above, the drug-drug interaction among the components of the proposed product and the formulation effect are considered to have been addressed, and such studies are not necessary. In addition, for such simple solutions, unless there is a known inherent food effect on the drug substance, assessment of food effect is not needed. However, in situations where the solutions do contain (b) (4) any excipients known to affect the bioavailability of the drug, in addition to the BE study mentioned, assessment of the effect of food on the proposed formulation is needed. For the conduct of the BE study and food effect study, you should refer to the Guidance for Industry entitled, "Bioavailability and Bioequivalence Studies

for Orally Administered Drug Products-General Considerations” and “Food-Effect Bioavailability and Fed Bioequivalence Studies”.

It is also recommended to use the reference listed drug (RLD) in the Orange Book (i.e., homatropine methylbromide and hydrocodone bitartrate combination syrup product from Hi Tech Pharma), as the reference hydrocodone product in the BE study.

If the above clinical pharmacology approach fails, a clinical development program with clinical efficacy and safety studies can be conducted to support the combination product.

#### CYPRESS’ QUESTIONS:

**Cypress’ reply to FDA’s Filing Communication for [REDACTED] (b)(4) Oral Solution (dated January 16, 2009):**

Potential Review Issue 1 (from page 1 of the Filing Communication)

*HCB:CPM:PSE (Treatment A) vs HYCODAN (Treatment D): The AUCs met the bioequivalence 80 -125% CI. From an efficacy perspective, the AUCs are the critical PK comparison particularly because no well-defined therapeutic range or C<sub>max</sub>-concentration threshold has been established for the HCB therapeutic effect. The C<sub>max</sub> parameter from the Cypress product was slightly outside the lower confidence interval (78.9%) which reduces the possibility of any safety concerns. Further, if the dose of the Cypress product were doubled to 10 mg, then based on dose-proportionality and linearity, the C<sub>max</sub> value from the Cypress product would be similar to that mentioned in the HYCODAN label for a 10 mg strength (22.66 ng/mL Cypress versus 23.6 ng/mL HYCODAN).*

Information Request 4 (from page 2 of the Filing Communication)

*Literature in the public domain (Yacobi, 1980) concludes there is NO interaction between CPM and PSE. Therefore, in combination with the Cypress study (S08-0179), the effect of CPM or PSE on the lack of systemic exposure to HCB has been addressed from Cypress’ perspective.*

**Does the above information provide sufficient support/justification to the Clinical Pharmacology reviewers to submit for the [REDACTED] (b)(4) filings or are there any other FDA considerations?**

**Cypress’ reply to FDA’s Filing Communication for REZIRA [REDACTED] (b)(4) Oral Solution (dated January 23, 2009):**

Information Request 3 (from page 2 of the Filing Communication)

*Cypress believes there are no DDI in the 3 component product because the AUCs met the bioequivalence criteria. See Potential Review Issue 1, below, for more information. In addition to the Yacobi paper showing no drug-drug interaction between CPM and PSE,*

*Cypress believes that bioequivalence has been established with 3 components, hence the declaration of bioequivalence for the 2 component product with an identical formulation holds true.*

***Is the Clinical Pharmacology reviewer in agreement?***



***Can the Clinical Pharmacology Reviewer comment on this Cypress reasoning?***



***Is this acceptable to the Clinical Pharmacology Reviewers?***

If you have any questions, call Philantha M. Bowen, Sr. Regulatory Management Officer, at 301-796-2466.

Drafted: Bowen/May 28, 2009

Initialed: Barnes/May 28, 2009  
Vaidyanathan/June 1, 2009  
Choe/June 1, 2009; June 9, 2009  
Sahajwalla/June 1, 2009  
Gilbert-McClain/June 2, 2009; June 9, 2009  
Chowdhury/June 9, 2009

Revised: Bowen/June 9, 2009

Finalized: Bowen/June 9, 2009

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/s/

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Philantha M Bowen  
6/9/2009 04:22:08 PM  
CSO



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** June 3, 2009

<b>To:</b> Dr. William Putnam, R.A.C.	<b>From:</b> Philantha Bowen, MPH, RN
<b>Company:</b> Cypress Pharmaceuticals c/o Beckloff Associates, Inc.	Division of Pulmonary and Allergy Drug Products
<b>Fax number:</b> 913-451-3846	<b>Fax number:</b> 301-796-9718
<b>Phone number:</b> 913-451-3955	<b>Phone number:</b> 301-796-2466
<b>Subject:</b> NDA 22-439 (b) (4) RE: CMC Comments	

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**Total no. of pages including cover:** 3

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**Comments:**

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**Document to be mailed:**  YES  NO

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THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

**NDA 22-439 Rezira-Plus**

(hydrocodone/chlorpheniramine/pseudoephedrine) Oral Solution (b) (4)

Your submissions dated November 6, 2008, and November 17, 2008, to NDA 22-439 (b) (4), are currently under review and we have the following CMC comment and recommendation:

1. (b) (4) in one of the drug substances, Chlorpheniramine Maleate, is identified as a potential structural alert for genotoxicity. Reduce the level of (b) (4) to no more than (b) (4)/day, or conduct a bacterial reverse mutation assay to qualify the proposed specification.
2. A deficiency letter for the DMF (b) (4) has been issued to (b) (4), the DMF holder.

If you have any questions, call Philantha Bowen, Senior Regulatory Management Officer, at 301-796-2466.

**Drafted by:** Bowen/June 1, 2009

**Initialed by:** Raggio/June 2, 2009  
Peri/June 2, 2009  
Markofsky/June 2, 2009  
Shen/June 2, 2009  
Al-Hakim/June 2, 2009

**Finalized by:** CHill/June 3, 2009

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/s/

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Carol F. Hill  
6/3/2009 10:18:01 AM  
CSO  
On Behalf of Philantha Bowen



NDA 22-439

**INFORMATION REQUEST LETTER**

Cypress Pharmaceutical, Inc.  
c/o Beckloff Associates, Inc.  
Commerce Plaza II, Suite 300  
7400 West 110<sup>th</sup> Street  
Overland Park, KS 66210

Attention: William Putman, Ph.D., R.A.C.  
Director, Executive Consultant

Dear Dr. Putman:

Please refer to your November 6, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b)(4) (hydrocodone, chlorpheniramine, and pseudoephedrine) Oral Solution.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission. We request a prompt written response in order to continue our evaluation of your NDA.

We have the following comments and information requests:

1. Several deficiencies were identified in hydrocodone bitartrate DMF (b)(4). The DMF holder was notified about the deficiencies in a letter dated December 18, 2008.
2. Establish specifications for (b)(4) impurity in hydrocodone bitartrate drug substance.
3. Establish specifications (b)(4) in hydrocodone bitartrate based on manufacturing capability shown by batch analysis data.
4. Lower the Class 2 OVIs/residual solvent limits in pseudoephedrine hydrochloride drug substance specification based on actual test results.
5. Submit stability and antimicrobial effectiveness testing results (b)(4).
6. Provide a justification for not establishing specifications for known degradants from chlorpheniramine maleate and pseudoephedrine hydrochloride drug substance or the release and stability testing of the drug product. Otherwise, establish specifications for the potential degradants.

7. Reduce the total impurity level of the drug product for both release and stability to levels supported by actual study data.
8. Submit validation protocol(s) for method SOP-QC-287.
9. Submit a copy of method SOP-QC-333 including the validation protocol and full validation report that supports accuracy and range of method SOP-QC-333.
10. Submit repeatability and intermediate precision validation results for method SOP-QC-334.
11. Submit an analytical method for detection and quantification of hydrocodone, chlorpheniramine and pseudoephedrine degradants in the drug product. If SOP-QC-287 is suitable, provide relevant validation data to support such claim.
12. Submit identity and physical chemical properties of substances that can potentially migrate from the drug product label or container into the drug product solution. In addition, provide information regarding the method suitability for detection and quantification of these substances. Provide leachable results and specifications for the drug product obtained from the above method. Provide relevant validation data to support the use of method SOP-QC-287.
13. Submit an explanation for the large assay variation observed in stability data across the different time points (e.g. the assay results of the three drug substance and the <sup>(b) (4)</sup> in the drug product have large variations from time point to time point, for example, the one and three month chlorpheniramine maleate assay values for Lot P08001 at 40°C/75% RH were <sup>(b) (4)</sup>).
14. Submit updated stability data to justify the proposed 2 year shelf life.
15. Submit the correct method reference or a copy of the test procedures used in the GSL certificate of analysis as identification test methods for Hydrocodone bitartrate, etc. Your COA referenced the relevant procedures as USP {A} and USP {B}, but such method can not be located in USP.
16. Clarify what USP procedure is used as USP (A) to identify pseudoephedrine hydrochloride drug substance in its release specification and update the pseudoephedrine hydrochloride drug substance specification table.

17. Report the related substances results in Table 3.2.S.4.4-2 (Batch Analysis for Hydrocodone Bitartrate, USP) based on ICH guideline Q3A (b) (4). Rectify the discrepancy between reported values for residual solvents in Table 3.2.S.4.4-2 and those in relevant COAs.
18. Submit the COA that supports the residual solvents results reported in Table 3.2.S.4.4-2 for chlorpheniramine maleate.
19. Optimize (b) (4) analysis method SOP-QC-334 to improve the peak shape of (b) (4) for better quantification accuracy, precision and reproducibility.
20. Correct your validation reports and submit the corrected relevant pages to the NDA application (e.g. your report for the verification of analytical method SOP-QC-301 and validation of method SOP-QC-287, the standard deviation and % RSD values were calculated based on two replicates in many cases. Note that at least three numbers should be used to calculate standard deviation and %RSD).
21. Submit detailed composition of (b) (4) used to prepare resolution standard in method SOP-QC-301 and include them in the method. If feasible, individual known impurities should be used to prepare the resolution solution at known impurity levels so that all known impurity peaks can be properly identified and accounted for.
22. Clarify if the analyzed samples are bracketed by standards for method SOP-QC-301. Amend the method to include a control standard (a second preparation of the standard solution) to assure the correct preparation of the standard solution used to quantify samples.
23. Verify that the relative response factor of (b) (4) in method SOP-QC-301 is (b) (4).
24. Submit the correct copy of method SOP-QC-334 and its validation report.
25. The specifications for total impurity acceptance criteria should be based on actual data from the long term stability study. Use of approved specifications from another drug product is not a scientific approach.
26. Weight loss testing is only needed for the (b) (4) professional sample.
27. Extension of expiration dating for the drug product should be handled in post-approval supplement.

28. Modify the drug product (16 fl. oz.) bottle label and sample carton to include lot/batch number and expiry information.
29. Modify the Package Insert to include the color of the solution in Section # 3, “Full Prescribing Information” and list the excipients alphabetically in Section # 11.

If you have any questions, call Philantha Bowen, Senior Regulatory Project Management Officer, at 301-796-2466.

Sincerely,

Ali Al-Hakim, Ph.D.  
Chief  
Office of New Drug Quality Assessment  
Division of Pre-Marketing Assessment I, Branch II  
Center for Drug Evaluation and Research

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/s/

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Ali Al-Hakim

4/30/2009 01:21:54 PM



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/s/

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Ali Al-Hakim

4/15/2009 04:44:47 PM



NDA 22-439

Cypress Pharmaceuticals, Inc.  
c/o Beckloff Associates, Inc.  
Commerce Plaza II, Suite 300  
7400 West 110<sup>th</sup> Street  
Overland Park, KS 66210

Attention: William C. Putman, Ph.D., R.A.C.  
Director, Executive Consultant  
Scientific Consulting

Dear Dr. Putman:

Please refer to your New Drug Application (NDA) dated November 6, 2008, received November 7, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hydrocodone, Chlorpheniramine, and Pseudoephedrine [Rx Only] containing 5 mg hydrocodone bitartrate, 4 mg chlorpheniramine, and 60 mg pseudoephedrine hydrochloride per 5 mL.

We acknowledge receipt of your January 29, 2009, correspondence, on January 30, 2009, notifying us that you are withdrawing your request for a review of the proposed proprietary name [REDACTED] (b)(4) Oral Solution. This proposed proprietary name request is considered withdrawn as of January 29, 2009.

We also acknowledge your Request for Proprietary Name Review dated, January 26, 2009, for the proposed proprietary name, [REDACTED] (b)(4)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Sean Bradley, R.Ph., Regulatory Project Manager, at (301) 796-1332. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager.

Sincerely,

*{See appended electronic signature page}*

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

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/s/

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Sandra Barnes

2/23/2009 06:16:28 PM



NDA 22-439

Cypress Pharmaceuticals, Inc.  
c/o Beckloff Associates, Inc.  
Commerce Plaza II, Suite 300  
7400 West 110<sup>th</sup> Street  
Overland Park, KS 66210

Attention: William C. Putman, Ph.D., R.A.C.  
Director, Executive Consultant  
Scientific Consulting

Dear Dr. Putman:

Please refer to your New Drug Application (NDA) dated November 6, 2008, received November 7, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hydrocodone, Chlorpheniramine, and Pseudoephedrine [Rx Only] containing 5 mg hydrocodone bitartrate, 4 mg chlorpheniramine, and 60 mg pseudoephedrine hydrochloride per 5 mL.

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We also acknowledge your Request for Proprietary Name Review dated, January 26, 2009, for the proposed proprietary name, (b)(4).

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Sean Bradley, R.Ph., Regulatory Project Manager, at (301) 796-1332. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager.

Sincerely,

*{See appended electronic signature page}*

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

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/s/

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Lydia McClain  
2/23/2009 08:19:52 PM  
Signed for Dr Badrul Chowdhury



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 22-439

Cypress Pharmaceutical, Inc.  
c/o Beckloff Associates, Inc.  
Commerce Plaza II, Suite 300  
7400 West 110<sup>th</sup> Street  
Overland Park, KS 66210

Attention: William Putman, Ph.D., R.A.C.  
Director, Executive Consultant

Dear Dr. Putman:

Please refer to your new drug application (NDA) dated November 6, 2008, received November 7, 2008, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for (b) (4) (hydrocodone, chlorpheniramine, and pseudoephedrine) Oral Solution.

We have completed our filing review and have determined that your applications are sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is standard. Therefore, the user fee goal date is September 7, 2009.

During our filing review of your application, we have identified the following potential review issues:

1. A preliminary assessment of the data indicates that the hydrocodone C<sub>max</sub> for your product is out of the 80-125% goal post of BE. The approval of the proposed product will be a review issue.
2. We note that you have provided only 3 months long term and accelerated stability data for the drug product and that you have not proposed a shelf life for the drug product. Based on the stability data in your NDA, you could potentially get a shelf life equal to the available real time data. It is inappropriate to set final specification based on the available stability data. This is a potential review issue as you will need to generate stability data to be able to assess trends in the attributes listed in your drug product specifications.

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

We also request that you submit the following information:

1. Submit information regarding previous marketing of your product, including safety information and marketing history.
2. Do not use the “TM” or “R” symbols after the drug names in 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.
3. Provide the formulation (components and composition) of the reference products (chlorpheniramine maleate and pseudoephedrine HCL) used in Study S08-0179. Be aware that a claim in terms of lack of drug-drug interaction between the components of your proposed product may not hold true, if the formulation of the references products for pseudoephedrine (PSE) and chlorpheniramine (CPM) are substantially different than that for (b) (4).
4. The pharmacokinetic (PK) study (S08-0179) as designed would not determine the effect of PSE and CPM on the systemic exposure of hydrocodone (HC). A comparison of (b) (4) vs. Hycodan (TRT A vs. D) may not address for the potential effect of CPM or PSE on the PK of HC due to the possibility of a confounded formulation effect. This information is required especially because NDA 22-442 (Rezira (b) (4): Hydrocodone, Pseudoephedrine Oral Solution) relies on the results of this study. Submit information on the potential effect of PSE and CPM on the PK of hydrocodone. You may rely on published information or conduct an additional PK study.
5. It is noted that information on the potential of food effect on the PK of (b) (4) was not included in the present submission. Reference is made to the pre-IND meeting for IND (b) (4) (01/14/2008) in which the Division recommended the assessment of food effect (b) (4).  
(b) (4)  
Submit information on the effect of food on the bioavailability (BA) of HC, PSE and CPM. You may choose to submit food effect information based on published literature (b) (4) or conduct an additional food effect study.
6. Provide references to direct food additive regulations for all the packaging materials (bottles, (b) (4) closures, etc.) that are in contact with the formulation.

7. An assessment of leachables in the drug product was not provided in the NDA. Submit the results of your evaluation of extractables and leachables from the container closure system and how you concluded that they do not exist and are not necessary for routine monitoring. We strongly recommend that you use appropriate analytical methods that are capable of monitoring and separating these compounds from other degradants and impurities in the drug product. Leachables specifications should be proposed when the data in your drug product have reached an asymptote.
8. Submit the CMC information (qualitative and quantitative composition, stability data etc.) of the comparison drug products: pseudoephedrine hydrochloride oral solution and chlorpheniramine maleate oral solution. If this information has already been submitted, provide a reference to the section and page number in your NDA.
9. Provide a quantitative and qualitative chemical composition of the grape flavor (b) (4). Alternately this information may be provided in an authorized Drug Master File (DMF).
10. Provide results of your Antimicrobial Effectiveness testing for your drug product.
11. Provide draft mock ups (100 % size) of the proposed carton, container labels.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application for pediatric patients birth to 12 years of age.

If you have any questions, call Philantha Bowen, Regulatory Project Manager, at (301) 796-2466.

Sincerely,

*{See appended electronic signature page}*

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

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/s/

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Badrul Chowdhury  
1/16/2009 04:57:29 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): Division Microbial Review Team David Hussong, Ph.D. and James McVey, Ph.D New Drug Microbiology Staff (OPS)		FROM: Philantha M. Bowen, Project Manager Division of Pulmonary and Allergy Drug Products ,HFD-570		
DATE January 15, 2009	IND NO.	NDA NO. 22-439, 22-442 (b) (4)	TYPE OF DOCUMENT N	DATE OF DOCUMENT 11/6/08, 11/7/08, 11/17/08, 11/19/08
NAME OF DRUG Rezira (b) (4)	PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG 1	DESIRED COMPLETION DATE April 6, 2009	
NAME OF FIRM: Cypress Pharmaceuticals				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): <div style="text-align: right;"><b>Microbiology</b></div>				
<b>II. BIOMETRICS</b>				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG SAFETY</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS: <i>The following assessments are requested:</i> Evaluate, from the microbiological perspective, the adequacy of the (b) (4) acceptance criteria (see 3.2.P.5.1), Microbial Limits test acceptance criteria (see 3.2.P.5.1), and the antimicrobial effectiveness testing justification (see 3.2.P.2.5). The non-sterile oral formulation (see 3.2.P.1) has Methyl Paraben and Propyl Paraben (b) (4). These applications located are located in the EDR.				
<b>PDUFA DATE: 9/7/09 NDA 22-439; 9/10/09 NDA 22-442 (b) (4)</b>				
SIGNATURE OF REQUESTER		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

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Philantha M Bowen  
1/16/2009 12:17:44 PM



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** January 6, 2009

<b>To:</b> Dr. William Putnam, R.A.C.	<b>From:</b> Philantha Bowen, MPH, RN
<b>Company:</b> Cypress Pharmaceuticals c/o Beckloff Associates, Inc.	Division of Pulmonary and Allergy Drug Products
<b>Fax number:</b> 913-451-3846	<b>Fax number:</b> 301-796-9718
<b>Phone number:</b> 913-451-3955	<b>Phone number:</b> 301-796-2466

**Subject:** NDA 22-439 and NDA 22-442 **Re:** Proprietary Name Review-Information Request

**Total no. of pages including cover:** 3

**Comments:**

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**Document to be mailed:**  YES  NO

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NDA 22-439 (b) (4)  
NDA 22-442 Rezira (b) (4)  
Cypress Pharmaceuticals, Inc.

Reference is made to your submissions dated November 26, 2008, and December 1, 2008, to NDA 22-439 and NDA 22-442, respectively for proprietary name review. We are reviewing the requests and have the following comments and request for information:



We appreciate a prompt written response in order to continue our evaluation of these submissions.

If you have any questions, contact Philantha Bowen, Regulatory Project Manager, at 301-796-2466.

**Drafted by:** Bowen/December 24, 2008

**Initialed by:** Barnes/December 31, 2008  
L. Toombs/January 6, 2009  
K. Arnwine/January 6, 2009

**Finalized by:** Bowen/January 6, 2009

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/s/

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Philantha M Bowen  
1/6/2009 09:55:58 AM  
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): <b>Division of Drug, Marketing, Advertising and Communication (DDMAC), HFD-42 PKLN Rm. 17B-17</b>		FROM: Philantha M. Bowen, Project Manager Division of Pulmonary and Allergy Drug Products, HFD-570		
DATE December 3, 2008	IND NO.	NDA NO. 22-439	TYPE OF DOCUMENT N	DATE OF DOCUMENT November 6, 2008
NAME OF DRUG (b) (4)	PRIORITY CONSIDERATION Standard		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE March 25, 2009
NAME OF FIRM: <b>Cypress Pharmaceuticals</b>				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Labeling Review				
<b>II. BIOMETRICS</b>				
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<b>III. BIOPHARMACEUTICS</b>				
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<b>IV. DRUG SAFETY</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:  This is a request for an evaluation and review of the labeling for NDA 22-439 (b) (4) Oral Solution. The labeling is in electronic format and is located in the EDR in the submission dated November 6, 2008. We have also submitted consults for other related NDAs: (b) (4) 22-442.				
<b>PDUFA DATE: September 7, 2009</b>				
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Philantha M Bowen  
12/3/2008 01:11:49 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): <b>OSE</b>		FROM: Philantha M. Bowen, Project Manager Division of Pulmonary and Allergy Drug Products ,HFD-570		
DATE December 2, 2008	IND NO.	NDA NO. 22-439	TYPE OF DOCUMENT N	DATE OF DOCUMENT November 6, 2008
NAME OF DRUG (b) (4)	PRIORITY CONSIDERATION Standard		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE March 25, 2009
NAME OF FIRM: <b>Cypress Pharmaceuticals</b>				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
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<b>II. BIOMETRICS</b>				
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<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:  This is a consult for a labeling review of (b) (4). The Package insert is electronic and located in the EDR in the submission dated November 6, 2008. We have also submitted consults for the other related NDAs: N 22-442 (b) (4)				
<b>PDUFA DATE: September 7, 2009</b>				
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Philantha M Bowen  
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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): <b>Controlled Substance Staff</b>		FROM: Philantha M. Bowen, Project Manager Division of Pulmonary and Allergy Drug Products ,HFD-570		
DATE December 3, 2008	IND NO.	NDA NO. 22-439 (b) (4) (b) (4) 22-442	TYPE OF DOCUMENT N	DATE OF DOCUMENT 11/6/08; 11/7/08; 11/17/08; 11/18/08
NAME OF DRUG Rezira (b) (4) (b) (4)	PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE March 27, 2009	
NAME OF FIRM: Cypress Pharmaceuticals				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
<b>II. BIOMETRICS</b>				
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<b>III. BIOPHARMACEUTICS</b>				
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<b>IV. DRUG SAFETY</b>				
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<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
<b>COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:</b> This is a consult for an evaluation of abuse liability and recommendations for drug scheduling for these products. The documents are electronic and located in the EDR in the submissions dated November 6, 2008, November 7, 2008, November 17, 2008, and November 18, 2008, for the NDAs listed in this consult.  (b) (4) (N-22-439 ;N-22-442) filing date January 7, 2009; <b>PDUFA Date</b> September 7 and 10, 2009, respectively. (b) (4)  The mid-cycle review meeting for these NDAs is scheduled for March 31, 2009 (b) (4) It is requested that the review for these applications be completed prior to the mid-cycle meetings.				
SIGNATURE OF REQUESTER		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND		
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NDA 22-439

**NDA ACKNOWLEDGMENT**

Cypress Pharmaceutical, Inc.  
c/o Beckloff Associates, Inc.  
Commerce Plaza II, Suite 300  
7400 West 110<sup>th</sup> Street  
Overland Park, KS 66210

Attention: William Putman, Ph.D., R.A.C.  
Director, Executive Consultant

Dear Dr. Putman:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: (b) (4) (hydrocodone, chlorpheniramine, and pseudoephedrine)  
Oral Solution

Date of Application: November 6, 2008

Date of Receipt: November 7, 2008

Our Reference Number: NDA 22-439

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 6, 2008 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, call Philantha Bowen, Regulatory Project Manager, at (301) 796-2466.

Sincerely,

*{See appended electronic signature page}*

Sandy Barnes  
Chief, Project Management Staff  
Division of Pulmonary and Allergy Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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Philantha M Bowen  
11/24/2008 05:26:08 PM  
Signed for Sandy Barnes

-DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			<b>REQUEST FOR CONSULTATION</b>	
TO (Division/Office): <b>PharmTox Review Team (Dr. Virgil Whitehurst)</b>			FROM: <b>Xiaobin Shen, Ph.D.</b> CMC Reviewer, DPAP in ONDQA/DPA1/Branch 2	
DATE: <b>Mar. 12, 2008</b>	NDA: <b>22439 (b)(4)</b> <b>and 22442</b>	TYPE OF DOCUMENT: NDA	DATE OF DOCUMENT 6-Nov-2008 to 18-Nov-2008	
NAME OF DRUG <b>REZIRA (b)(4)</b> <b>(b)(4)</b>	PRIORITY CONSIDERATION: S	CLASSIFICATION OF DRUG: 3	DESIRED COMPLETION DATE May 30, 2009	
NAME OF FIRM: <b>Cypress Pharmaceuticals, Inc.</b>				
<b>REASON FOR REQUEST: Evaluation of</b> The safety of the levels of <b>(b)(4)</b> impurity exists in the drug substance hydrocodone bitartrate <b>(b)(4)</b> <b>(b)(4)</b>				
<b>COMMENTS/SPECIAL INSTRUCTIONS: See below.</b>  <b>(b)(4)</b> NDAs are in EDR. The relevant pages are shown attached.  Thanks!  Xiaobin.				

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FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**Meeting Type:** Type B  
**Meeting Category:** Pre-IND  
**Meeting Date and Time:** January 14, 2008 12:30 – 2:00 pm EST  
**Meeting Location:** Building 22, Conference Room 1419  
**Application Number:** (b) (4)  
**Product Name:** (b) (4)  
Hydrocodone/Pseudoephedrine Oral Solution  
Hydrocodone/Chlorpheniramine/Pseudoephedrine Oral Solution

**Received Briefing Package** December 7, 2007  
**Sponsor Name:** Cypress Pharmaceutical, Inc.  
**Meeting Requestor:** Robert L. Lewis II  
Director of Product Development  
**Meeting Chair:** Badrul A. Chowdhury, M.D., Ph.D., Director  
Division of Pulmonary and Allergy Products  
**Meeting Recorder:** Philantha M. Bowen, MPH, R.N.  
Sr. Regulatory Management Officer

**Meeting Attendees:**  
**FDA Attendees**  
Office of Drug Evaluation II  
Badrul A. Chowdhury, M.D., Ph.D., Division Director, Division of  
Pulmonary and Allergy Products

Philantha M. Bowen, M.P.H., RN, Senior Regulatory Management Officer, Division of Pulmonary and Allergy Products

Charles E. Lee, M.D., Clinical Team Leader, Division of Pulmonary and Allergy Products

Xu Wang, M.D., Clinical Reviewer, Division of Pulmonary and Allergy Products

C. Joe Sun, Ph.D., Pharmacology/Toxicology Supervisor, Division of Pulmonary and Allergy Products

Jean Wu, Ph.D., Pharmacology/Toxicology Reviewer, Division of Pulmonary and Allergy Products

Office of New Drug Quality Assessment

Prasad Peri, Ph.D., Pharmaceutical Assessment Lead, Division of Pre-Marketing Assessment I, Branch II

Office of Clinical Pharmacology

Wei Qiu, Ph.D., Acting Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 2

Suarez, Sandra, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 2

Office of Regulatory Policy

Michael D. Jones

Brian L. Pendleton, Regulatory Counsel

**Sponsor Attendees**

Cypress Pharmaceutical

Robert L. Lewis, Director of Product Development

Janet DeLeon, Associate Director of Product Development

(b) (4)

## 1.0 BACKGROUND

Cypress Pharmaceutical, Inc. submitted a Type B meeting request dated October 23, 2007, to seek guidance on the development program for (b) (4)

(b) (4) hydrocodone/pseudoephedrine oral solution, and hydrocodone/chlorpheniramine/pseudoephedrine oral solution. The briefing package, dated December 7, 2007, was reviewed by the Division. On January 10, 2008, the Division responded to Cypress' questions via facsimile. The content of the fax is printed below.

Any discussion that took place at the meeting is captured directly under the original response including any changes in our original position. Cypress' questions are in ***bold italics***; FDA's response is in *italics*; and the discussion is in normal font.

## 2.0 QUESTIONS

### 2.1 QUESTION 1

#### Question 1:

***Does the Agency agree that the 505(b)(2) submission route is appropriate with the cited Reference NDA Drugs and OTC Monographs as follows?***

#### FDA Response:

*A 505(b)(2) NDA submission would be an acceptable approach based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/cder/guidance/index.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408).*

*If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for a listed drug, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug. In this case, you should establish a "clinical bridge" between your proposed drug product and the listed drug (e.g., via comparative bioavailability data) to demonstrate that reliance is appropriate. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.*

*You should cite the listed drugs on whose findings you wish to rely in support of the 505(b)(2) submission. Also, an approved hydrocodone antitussive drug product (e.g., Hycodan) and OTC*

Monograph drug products should be included as comparators in your clinical pharmacology studies (see our response to Question 3).

The proposed dosage of pseudoephedrine for your products (adults (b) (4)) exceeds the 24-hour dose specified by the OTC Monograph (adults and children  $\geq 12$  years old: 60 mg every 4 to 6 hours, NTE 240 mg in 24 hours; children 6 to 12 years old: 30 mg every 4 to 6 hours, NTE 120 mg in 24 hours). You will not be able to rely on the OTC Monograph to support the safety of your products containing pseudoephedrine. Clinical trials will be necessary to support the safety of your proposed pseudoephedrine doses. Alternatively, you may revise the dosage instruction so that the pseudoephedrine hydrochloride dose is NTE 240 mg (b) (4) for adults (b) (4).

Your proposed indication for products containing chlorpheniramine is not consistent with the OTC monograph. The OTC monograph indication for chlorpheniramine is "temporary relief of runny nose, sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever" (which may be followed by one or both of the following: "or other upper respiratory allergies" or "(allergic rhinitis)") (whereas your proposed indication refers to (b) (4)).

#### Discussion:

Cypress began the discussion by informing the FDA that the pseudoephedrine dosing interval was incorrectly stated in the briefing package. The sponsor proposes that the pseudoephedrine labeling would read "not to exceed 4 doses in 24 hours." Thus, the total dose of the product ingredients would comply with the OTC monograph.

Cypress asked the FDA to clarify the comment regarding their proposed indication for products containing chlorpheniramine and the OTC monograph. The FDA responded that indication must include the OTC language for the antihistamine indication. The FDA referred Cypress to the CFR for OTC monograph products.

## 2.2 QUESTION 2

### Question 2:

***Does the Agency concur that the available regulatory information cited fully supports the safety and efficacy of the active ingredients (b) (4) pseudoephedrine hydrochloride, and chlorpheniramine maleate, i.e., the OTC monograph for (b) (4) antihistamine drug products, and nasal decongestant drug products? As previously noted in this submission, (b) (4), chlorpheniramine maleate is an accepted antihistamine (21 CFR 314.12) (b) (4), and pseudoephedrine hydrochloride are accepted nasal decongestants (21 CFR 341.20) in the OTC Drug Monograph 21 CFR 341 - Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-The-Counter Human***

***Use. These ingredients have undergone regulatory review through the OTC monograph process.***

FDA Response:

*Refer to our response in question 3.*

Discussion:

There was no discussion on question 2.

### 2.3 QUESTION 3

Question 3:

***Does the Agency concur that the available regulatory information for hydrocodone bitartrate fully supports the safety and efficacy of the ingredient for use in the combination products referenced in this submission? (Hydrocodone bitartrate is a generally recognized antitussive with efficacy established in DESI Notice #5213, dated June 1, 1982. Hydrocodone was not included in the OTC Monograph process and is available on a prescription only basis (Rx Only). The opioid, hydrocodone bitartrate, has been the subject of numerous NDAs approved by the Agency for its proposed therapeutic use as an antitussive and for pain.)***

FDA Response to Questions 2 and 3:

*We do not concur.*

- You will need to address the proposed pseudoephedrine dose for your products (Refer to our response to Question 1).*
- You need to demonstrate that your proposed products are bioequivalent to an approved hydrocodone antitussive drug product (e.g., Hycodan) and OTC Monograph drug products by conducting comparative bioavailability studies.*

Discussion:

Cypress questioned the FDA regarding the need for a bioequivalence (BE) study to Hycodan, in order to determine the bioavailability of hydrocodone from the proposed product. (b) (4)

[REDACTED]

[REDACTED] (b) (4)

## 2.4 QUESTION 4

### Question 4:

*Cypress believes that the reference to the approved NDA products and the OTC monograph evaluation is sufficient to meet the preclinical requirements for (b) (4) pseudoephedrine hydrochloride, chlorpheniramine maleate, and hydrocodone bitartrate. Does the agency concur? Will any additional preclinical safety studies be required for the IND/NDA submission?*

### FDA Response:

*Yes, we agree that no additional preclinical studies are required for the IND/NDA submission based on the approved NDA products and OTC Monograph. However, the maximum dosage proposed for pseudoephedrine is above the maximum OTC Monograph dose. (Refer to the clinical response to Question 1). If the pseudoephedrine dosage in any clinical study(ies) is higher than the monograph dose, provide evidence/justification to support the proposed pseudoephedrine dose in your IND submission.*

### Additional preclinical comment:

*Monitor impurities and degradation products structurally similar to hydrocodone, since some have been identified as having structural alerts for genetic toxicity. If such impurities and degradations exceed (b) (4) day total intake by the subject, these will have to be qualified by genotoxicity testing. In addition, if impurities and degradations exceed the ICH Qualification Thresholds for drug substances (ICH Q3A(R)) and drug products (ICH Q3B(R)), these will have to be qualified by a 90-day repeated-dose toxicity study.*

### Discussion:

Cypress commented that hydrocodone was not a reproductive or mutagenic concern and requested that the FDA clarify whether the comment was specific to one particular impurity that was present and qualified in an approved drug product of the same drug substance supplier. The FDA responded that the comment addresses all impurities or degradation products with a

structure similar to hydrocodone. If such impurities or degradation products have been identified and/or qualified, Cypress should submit the information for review in the NDA.

## 2.5 QUESTION 5

### Question 5:

*Cypress believes that because the (b) (4) drug products are immediate release oral products, the pharmacokinetic requirements are minimal. Cypress proposes to conduct (b) (4) bioavailability studies to demonstrate the in vivo availability of the active ingredients from the (b) (4) products. These (b) (4) studies will determine the in vivo pharmacokinetic characteristics of the drug products in 12 to 24 normal healthy subjects. Does the Agency concur with this proposal?*

### FDA Response:

(b) (4)

*The waiver of BE requirements for your proposed oral solution products cannot be granted (b) (4). Therefore, you need to conduct in vivo BE studies for the following proposed products using the appropriate reference for each active ingredient. These studies may also provide information for potential drug-drug interaction among the components:*

- **Hydrocodone, Chlorpheniramine, and Pseudoephedrine Oral Solution.**

*The waiver of BE requirements for the following proposed oral solution products may be granted based on the results of the above mentioned BE studies provided no major changes in the formulation (inactive ingredients) has occurred:*

- **Hydrocodone and Pseudoephedrine Oral Solution**

(b) (4)

*The waiver of BE requirements for all your proposed oral solution products may be granted (b) (4). However, you still need to conduct in vivo BA studies and to assess the potential for drug-drug interactions. The drug-drug interaction information may be provided from the literature or by conducting pharmacokinetic drug-drug interaction studies.*

### Discussion:

(b) (4) Cypress proposed to conduct (b) (4) bioequivalence studies and to provide available literature for the drug-drug interactions (DDI). The FDA commented that (b) (4) was a

recommendation. The Agency agreed with the sponsor's proposal then added that one *in vivo* BE study may be sufficient to support approval of the (b) (4) proposed solution products (b) (4)

The waiver of the *in vivo* BE requirements for the remaining proposed solution formulation could be granted provided that there are no major changes in the formulations of all the proposed products. Cypress verbalized their understanding that the following studies will need to be conducted: (b) (4) a BE study for one of the solution products, (b) (4), to the reference product (b) (4)

The FDA acknowledged Cypress' understanding of the studies that need to be conducted, clarifying that the BE study for the solution product of choice (b) (4), should emphasize the effect on hydrocodone against the reference product. Cross-study comparisons would not be acceptable. In addition, Cypress will also need to assess drug-drug interactions for all the proposed products.

Cypress proposes to submit (b) (4) INDs for the products ((b) (4) the solutions) requiring the BE/BA studies as discussed above. The FDA agreed to respond to the sponsor in a post meeting comment as to whether an IND would need to be submitted (b) (4)

#### Post Meeting Comment:

On January 16, 2008, the sponsor sent an e-mail requesting clarification of the Division's position on *in vivo* studies required as follows:

- (1) (b) (4)
- (2) A BE/BA study for one of the solution products (b) (4) in which the bioequivalence of hydrocodone is measured versus Hycodan syrup and the BA parameters of chlorpheniramine and pseudoephedrine are determined
- (3) The potential of drug-drug interactions should be addressed
- (4) The potential of a food effect for hydrocodone should be addressed

Cypress also requested clarification on the food effect requirements for hydrocodone in the oral solution product. Cypress believes that there should be no food effect requirement for the oral solution study.

In general, the agency agrees with the sponsor's statements (1)-(4). (b) (4)

The agency agrees that no food effect study need to be conducted with the proposed oral solution formulations.

(b) (4) INDs would be the minimum number required (b) (4) assuming that published information on drug-drug interaction is sufficient to address each combination of ingredients. However, if there is a need to conduct *in vivo* studies to address DDI due to lack of published information on this issue, the sponsor may need to submit (b) (4) INDs.

## 2.6 QUESTION 6

### Question 6:

*Does the Agency require a survey of the available clinical and nonclinical literature, FDA adverse event database (NTIS), World Health Organization (WHO) adverse event database, international regulatory actions, and past Agency's findings in support of the safety and efficacy of the proposed drug products? Will a safety update report for the listed drugs be required?*

### FDA Response:

*Yes, the Agency requires a survey of the available clinical and nonclinical literature as you have described. A safety update report for the listed drugs is required as well.*

### Discussion:

There was no discussion on question 6.

## 2.7 QUESTION 7

### Question 7:

*Cypress plans to seek a waiver from the requirement to conduct pediatric studies under the Pediatric Research Equity Act. This drug product is not recommended for use in patients under 6 years of age, should not be used in a substantial number of pediatric patients, and prescriptions should be significantly less than the 50,000-prescription threshold cited in previous FDA documents as a barometer to determine if the product would likely be used in a significant number of pediatric patients. Please specify. Does the Agency concur that a waiver is attainable?*

### FDA Response:

*Yes, we concur that a waiver may be appropriate. If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver when submitting your NDA application. Include supporting information and documentation in accordance with the provisions of 21 CFR 314.55. You may find more information on CDER's Pediatric Drug Development Page (<http://www.fda.gov/www.fda.gov/cder/pediatric/>) and in the Draft Guidance for Industry: How to Comply with the Pediatric Research Equity Act (<http://www.fda.gov/cder/guidance/6215dft.pdf>).*

### Discussion:

There was no discussion on question 7.

## 2.8 QUESTION 8

### Question 8:

**Regarding user fees for the 505(b)(2) applications, please indicate for which applications a user fee will be required. For all (b) (4) applications, clinical data will not be required ( (b) (4) NDAs will contain bioavailability and CMC data, (b) (4) ).**

### FDA Response:

*The Division does not assess or waive user fees. However, all 505(b) applications (505(b)(1) or 505(b)(2) applications), are eligible for the assessment of an application fee, unless otherwise exempted or waived. In order to establish how much of a fee should be assessed, one has to determine if clinical data, other than bioavailability or bioequivalence data, (note – literature could be considered clinical data), with respect to safety or efficacy is required for approval. We recommend that you contact Michael Jones, User Fee staff, in the Office of Regulatory Policy for questions about user fees. Additional information on user fees may be found in the Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees (December 30, 2004), available at <http://www.fda.gov/cder/guidance/5469fnl.pdf>.*

### Discussion:

Cypress requested that the FDA clarify which applications would be subject to user fees. In addition, questioned as to whether drug-drug interactions was considered to be outside of a BE/BA study. The FDA responded that, at least, a half user fee amount should be expected for each application. Applications for which clinical data (other than bioavailability or bioequivalence) with respect to safety or efficacy is required for approval, would be assessed a full fee. Clinical data could be their own data or clinical data that is provided by literature. The Division will need to determine which NDAs will require clinical data for approval (BE/BA data, however, is not considered clinical data). In terms of literature provided for drug-drug interactions, the FDA will need to review and evaluate this situation. However, if the literature provided is being used to support safety and/or efficacy, beyond that of BE/BA, then the full user fee would apply. Therefore, each application should be expected to be assessed, at least, a half user fee. If any application requires clinical data (other than BE or BA), for approval, then a full user fee would be assessed.

## 2.9 QUESTION 9

### Question 9:

**It is Cypress's intention to submit (b) (4) new drug applications for the drug products. Each application will contain three submission exhibit batches, testing and stability data for each batch. Stability data reporting at time of filing will consist of 3 months or room**

*temperature (25 C, 60% RH) data and 3 months of accelerated (40 C, 75% RH) data. Does the Agency concur?*

FDA Response:

*We note that although the starting materials (APIs) are approved previously in different drug products, your formulations are different. Hence, the shelf life of your drug products will be dependent on the stability data that you provide in your NDAs. Note that if real time stability data submitted in the NDA is 3 months, a potential shelf life of (b) (4) for the drug products could be approved. Refer to the following documents: ICH Q1A(R2): Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products. ICH Q1E: Guidance for Industry: Evaluation of Stability Data*

Additional CMC Comments:

1. (b) (4)
2. *Provide the CMC information (e.g., qualitative and quantitative composition, certificates of analyses, etc.) for all colors, flavors, (b) (4) used in your drug products in your INDs. Alternately provide this information in an appropriately authorized Drug Master Files (DMFs).*
3. *Refer to the following regulations in preparing your IND submissions: 21 CFR 312.23.*
4. *Refer to the following guidance document available at the FDA web site: Guidance for Industry INDs for Phase 2 and Phase 3 Studies Chemistry, Manufacturing, and Controls Information.*

Discussion:

Cypress requested that the FDA address their proposal of submitting 3 months of accelerated data. Cypress plans to provide additional stability data, such that there will be 6 months of accelerated data and 9-12 months of room temperature data for review. Thus, such data should justify a 24 month expiration for the product.

The FDA responded that each formulation is unique and the shelf life will be based on the data. A rationale for 24 month expiration with the proposed 9-12 months of long term stability data will be a review issue. This will depend on the robustness of the stability data, when the data is submitted. Cypress should provide the long term and accelerated data as early in the review process as possible. The review of stability data submitted after the NDA submission, however, may or may not be evaluated depending on the workload of the reviewers at that time.

Cypress asked the FDA to comment on a priority review for their proposed NDAs. The FDA recommended that Cypress submit their justification for a priority review along with their NDA submissions. In terms of the IND, Cypress commented that they plan to submit the INDs shortly.

Post-Meeting Comments:

1. As the drug development progresses, evaluate the potential for leachables in your drug product. Adequate pharmacology/toxicology evaluation for safety of the observed leachables will be required.
2. As the development progresses, incorporate a quantitative test for color (e.g., APHA), and weight loss of the drug product.

The acronym APHA stands for American Public Health Association. APHA is the name used in Hunter Lab systems. A detailed description of solution preparation and measurement procedures may be found in ASTM Designation D1209, "Standard Test Method for Color of Clear Liquids (Platinum-Cobalt Scale)."

3. Provide letters of authorization to DMFs for the drug substances in your IND. Similarly, provide letters of authorization for DMFs for the container closure components.

**3.0 ISSUES REQUIRING FURTHER DISCUSSION**

There were no issues requiring further discussion

**4.0 ACTION ITEMS**

Refer to FDA's post meeting comments for questions 5 and 9.

**5.0 ATTACHMENTS AND HANDOUTS**

There were no attachments or handouts for this meeting

**Drafted by:** Bowen/January 22, 2008

**Initialed by:** Michael Jones/January 23, 2008

Pendleton/January 23, 2008

Wu/January 29, 2008

Sun/January 29, 2008

Peri/January 22, 2008

Al-Hakim/January 22, 2008

Suarez/January 29, 2008

Wei/January 29, 2008

Wang/January 29, 2008

Lee/January 29, 2008

Chowdhury/February 5, 2008

**Finalized by:** Bowen/February 6, 2008

Linked Applications

Sponsor Name

Drug Name

IND (b) (4)

CYPRESS PHARM

(b) (4)  
ORAL SOLTN

**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  
02/06/2008