

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**204307Orig1s000**

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

## EXCLUSIVITY SUMMARY

NDA # 204307

SUPPL #

HFD #

Trade Name Vituz

Generic Name hydrocodone bitartrate and chlorpheniramine maleate

Applicant Name Cypress Pharmaceuticals, Inc.

Approval Date, If Known 02/20/2013

### 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 X 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 X

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 X

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

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

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 X

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 X NO

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

NDA# 22439	Zutripro
NDA# 22442	Rezira
NDA# 2531	Hycodan
NDA# 19111	Tussionex Pennkinetic

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:

(b) For each investigation not carried out under an IND or for which the applicant was not

identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !  
!  
YES  ! NO   
Explain: ! Explain:

Investigation #2 !  
!  
YES  ! NO   
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:

=====

Name of person completing form: Leila P. Hann  
Title: Regulatory Project Manager  
Date: February 20, 2013

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

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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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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LEILA P HANN  
02/20/2013

LYDIA I GILBERT MCCLAIN  
02/20/2013

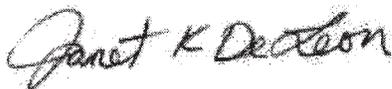
### 1.3.3 Debarment Certification

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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Janet K. DeLeon, RAC  
Director of Product Development  
Cypress Pharmaceutical, Inc.  
Madison, MS

April 23, 2012

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Date

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 204307 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Vituz Established/Proper Name: hydrocodone bitartrate and chlorpheniramine maleate Dosage Form: oral solution		Applicant: Cypress Pharmaceuticals Agent for Applicant (if applicable):
RPM: Leila P. Hamm		Division: DPARP
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p><b><u>NDA and NDA Efficacy Supplements:</u></b></p> <p>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> </div> <div style="width: 50%;"> <p><b><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></b></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s):</p> <p>Hycodan (NDA5213)</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>This product is a combination of the listed drug and chlorpheniramine (OTC monograph).</p> <p><input type="checkbox"/> This application does not reply upon a listed drug.  <input type="checkbox"/> This application relies on literature.  <input checked="" type="checkbox"/> This application relies on a final OTC monograph.  <input type="checkbox"/> This application relies on (explain)</p> <p><b><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> 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>X No changes    <input type="checkbox"/> Updated    Date of check: 02/20/2013</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> </div> </div>		
❖ Actions		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>February 24, 2013</u></li> </ul>		x AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		x None

<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.

<sup>2</sup> For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).



❖ 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 checked="" 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>4</sup>	Yes
<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> )	X Included
Documentation of consent/non-consent by officers/employees	X Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) Approval 02/20/2013
<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>	02/20/2012
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	04/24/2012
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	

<sup>4</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> </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>	02/13/2013
<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> <li>• Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</li> </ul> </li> </ul>	07/24/2012 and Denied 07/24/2012 10/26/2012 and Accepted 10/26/2012
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input checked="" type="checkbox"/> RPM 02/07/2013 <input checked="" type="checkbox"/> DMEPA 07/24/2012 <input type="checkbox"/> DMPP/PLT (DRISK) <input checked="" type="checkbox"/> ODPD (DDMAC) 10/04/2012 <input checked="" type="checkbox"/> SEALD 02/14/2013 <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>5</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> </ul>	RPM Filing Review 02/06/2013
<ul style="list-style-type: none"> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> </ul>	<input type="checkbox"/> Not a (b)(2) 01/30/2013
<ul style="list-style-type: none"> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	<input type="checkbox"/> Not a (b)(2) 02/20/2013
<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
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>10/10/2012</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> </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>5</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Outgoing communications ( <i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i> )	11/21/2012 10/19/2012 10/11/2012 08/01/2012 07/06/2012 05/08/2012
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing ( <i>indicate date of mtg</i> )	x No mtg
• If not the first review cycle, any end-of-review meeting ( <i>indicate date of mtg</i> )	x N/A or no mtg
• Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )	x No mtg
• EOP2 meeting ( <i>indicate date of mtg</i> )	x No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) ( <i>indicate dates of mtgs</i> )	
❖ Advisory Committee Meeting(s)	x 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> )	X None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 02/20/2013
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 01/31/2013
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input type="checkbox"/> None two
<b>Clinical Information<sup>6</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	Concurrence on Clinical review 01/18/2013
• Clinical review(s) ( <i>indicate date for each review</i> )	01/18/2013, 07/25/2012
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	X 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> )	01/18/2013 Page 17 of Clinical Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	X None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	X Not applicable
❖ 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> )	X None

<sup>6</sup> Filing reviews should be filed with the discipline reviews.

❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)	X None requested
<b>Clinical Microbiology</b> X 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> X 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)	X None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None Concurrence on 10/31/2012
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 10/31/2012, 07/02/2012
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	X None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	X None
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> None 08/02/2012
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 08/01/2012, 06/12/2012
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	X None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	X No carc
❖ ECAC/CAC report/memo of meeting	X None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	X 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)	X None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None Concurrence on 01/03/2013
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	<input type="checkbox"/> None 01/03/2013, 06/08/2012
❖ Microbiology Reviews X NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review) <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (indicate date of each review)	<input type="checkbox"/> Not needed 11/01/2012
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	X None

❖ 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> )	01/02/2013
<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</i> ) ( <i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>7</sup></i> )	Date completed: 01/02/2013 <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</i> ) ( <i>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>7</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.

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/s/  
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LEILA P HANN  
02/20/2013



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

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** February 20, 2013

<b>To:</b> Janet DeLeon, Director of Product Development	Leila P. Hann <b>From:</b> Regulatory Management Officer
<b>Company:</b> Cypress Pharmaceutical	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Fax number:</b> 913-681-0669	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 913-681-0667	<b>Phone number:</b> 301-796-3367

**Subject:** NDA 204307 (Vituz) Information Request

**Total no. of pages including cover:** 16

**Comments:**

**Document to be mailed:** YES xNO

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We are currently reviewing your NDA for Vituz. Submit your concurrence to the revised labeling changes shown in the attached marked up PI.

Please submit a response by February 20, 2013 at NOON so that we can complete our review. A formal submission will also need to be made to the NDA shortly thereafter. If you have any questions, please contact Leila P. Hann, Regulatory Program Manager, at 301-796-3367.

Drafted by: L. Hann/ February 20, 2013  
Cleared by: S. Barnes/ February 20, 2013  
Finalized by: L. Hann/ February 20, 2013

13 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/  
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LEILA P HANN  
02/20/2013



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 Office of Drug Evaluation II

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** February 15, 2013

<b>To:</b> Janet DeLeon, Director of Product Development	Leila P. Hann <b>From:</b> Regulatory Management Officer
<b>Company:</b> Cypress Pharmaceutical	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Fax number:</b> 913-681-0669	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 913-681-0667	<b>Phone number:</b> 301-796-3367

**Subject:** NDA 204307 (Vituz) Information Request

**Total no. of pages including cover:** 17

**Comments:**

**Document to be mailed:** YES xNO

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We are currently reviewing your NDA for Vituz. Additional labeling changes may be forthcoming. Submit revised labeling incorporating changes shown in the attached marked up PI (the changes are also listed below for clarity). These changes have been made to keep up with regulations and current best practices.

1. Decrease margin at top of Highlights to ½ inch.
2. Insert cross reference (i.e., "(1.1)") after the statement "Not indicated for pediatric patients under 18 years of age" under the Indications and Usage heading.
3. Remove Recent Major Changes (RMC) heading from Highlights. RMCs are only applicable to NDA/BLA supplements.
4. Change drug name to all upper case letters in Highlights Limitation Statement (i.e., "VITUZ"). SEALD recommends deletion of "Oral Solution" from the Highlights Limitation Statement.
5. Insert horizontal line in between Table of Contents and Full Prescribing InformationI.
6. There is no patient labeling for this product. Remove reference to FDA-approved patient labeling at the beginning of Section 17.
7. Adjust columns in Highlights to be as close to equal length as possible.
8. Delete [REDACTED] (b) (4) from the top of Highlights.
9. Insert a line of white space in between the Highlights limitation statement and the product title.
10. Correct the product title to read, "**VITUZ (hydrocodone bitartrate and chlorpheniramine maleate) oral solution, CIII**"
11. At the end of Highlights, insert a line of white space above the revision date and right justify the revision date.
12. Modify the established pharmacologic class statement in the Indications and Usage header in Highlights to the following:

Vituz® Oral Solution is a combination of hydrocodone bitartrate, [REDACTED] (b) (4) [REDACTED] an antitussive, and chlorpheniramine maleate, a [REDACTED] (b) (4) histamine-1 (H1) receptor antagonist [REDACTED] (b) (4) indicated for relief of cough and symptoms associated with upper respiratory allergies or a common cold (1.1).

Please submit a response by February 19, 2013 at NOON so that we can complete our review. If you have any questions, please contact Leila P. Hann, Regulatory Program Manager, at 301-796-3367.

Drafted by: L. Hann/ February 15, 2013  
Cleared by: S. Barnes/ February 15, 2013  
Finalized by: L. Hann/ February 15, 2013

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LEILA P HANN  
02/15/2013



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**FACSIMILE TRANSMITTAL SHEET**

**DATE:** February 13, 2013

<b>To:</b> Janet DeLeon, Director of Product Development	Leila P. Hann <b>From:</b> Regulatory Management Officer
<b>Company:</b> Cypress Pharmaceutical	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Fax number:</b> 913-681-0669	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 913-681-0667	<b>Phone number:</b> 301-796-3367

**Subject:** NDA 204307 (Vituz) Information Request

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

**Comments:**

**Document to be mailed:** YES xNO

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Your application is currently under review and we have the following information requests regarding PMR timelines:

Conduct a study to assess the pharmacokinetics of each Vituz drug component (hydrocodone and chlorpheniramine) in approximately 25-35 children ages 6-17 years with symptoms of the common cold. The study can be conducted with a formulation containing hydrocodone, chlorpheniramine, and pseudoephedrine. The results of this study will be used to determine the appropriate dose of the combination product to evaluate in a safety study in children ages 6-17 years.

Final Protocol Submission:	March 8, 2013
Trial Completion:	December 31, 2013
Final Report Submission:	June 30, 2014

Conduct a study to assess the safety of Vituz (hydrocodone and chlorpheniramine) in approximately 400-450 children ages 6-17 years with symptoms of the common cold. The study can be conducted with a formulation containing hydrocodone, chlorpheniramine, and pseudoephedrine. The dose used in this study will be based upon the pharmacokinetic study in children ages 6-17 years.

Final Protocol Submission:	September 30, 2014
Trial Completion:	December 31, 2015
Final Report Submission:	September 30, 2016

Please submit your concurrence by February 14, 2013 at NOON so that we can complete our review. If you have any questions, please contact Leila P. Hann, Regulatory Program Manager, at 301-796-3367.

Drafted by: L. Hann/ February 13, 2013  
Cleared by: S. Barnes/ February 13, 2013  
X. Wang/ February 13, 2013  
A. Durmowicz/ February 13, 2013  
S. Seymour/ February 13, 2013  
Finalized by: L. Hann/ February 13, 2013

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LEILA P HANN  
02/13/2013



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**FACSIMILE TRANSMITTAL SHEET**

**DATE:** February 11, 2013

<b>To:</b> Janet DeLeon, Director of Product Development	Leila P. Hann <b>From:</b> Regulatory Management Officer
<b>Company:</b> Cypress Pharmaceutical	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Fax number:</b> 913-681-0669	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 913-681-0667	<b>Phone number:</b> 301-796-3367

**Subject:** NDA 204307 (Vituz) Information Request

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

**Comments:**

**Document to be mailed:** YES xNO

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Your application is currently under review and we have the following information requests regarding labeling:

1. Remove the adverse reactions listed below, as shown in the attached marked up labeling as they are not related to this product.



2. Revise all labeling, including the carton and container, with the approved proprietary name in type case.
3. The initial year of approval for this product is 1987 which is the initial year of approval for Tussionex Pennkinetic (NDA19111).

Please submit a response by February 13, 2013 at NOON so that we can complete our review. If you have any questions, please contact Leila P. Hann, Regulatory Program Manager, at 301-796-3367.

Drafted by: L. Hann/ February 11, 2013  
Cleared by: S. Barnes/ February 11, 2013  
X. Wang/ February 11, 2013  
A. Durmowicz/ February 11, 2013  
Finalized by: L. Hann/ February 11, 2013

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LEILA P HANN  
02/11/2013



Food and Drug Administration  
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**FACSIMILE TRANSMITTAL SHEET**

**DATE:** November 21, 2012

<b>To:</b> Janet DeLeon, Director of Product Development	Leila Hann <b>From:</b> Regulatory Management Officer
<b>Company:</b> Cypress Pharmaceutical	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Fax number:</b> 913-681-0669	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 913-681-0667	<b>Phone number:</b> 301-796-3367

**Subject:** NDA 204307 (Vituz) Labeling Edits

**Total no. of pages including cover:** 16

**Comments:**

**Document to be mailed:** YES xNO

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Your NDA 204307 submission is currently under review and we request the following labeling revisions:

The labeling edits in the attached document are provided in the tracked change format. We may have additional comments as our review proceeds. Submit revised labeling incorporating these comments as soon as possible via email to [leila.hann@fda.hhs.gov](mailto:leila.hann@fda.hhs.gov). Your response will also have to be submitted officially to the NDA supplement shortly thereafter.

If you have any questions, please contact Leila Hann, Regulatory Program Manager, at 301-796-3367.

Drafted: X. Wang/ November 13, 2012  
Cleared: A. Durmowicz/ November 13, 2012  
S. Barnes/ November 21, 2012  
Finalized: L. Hann/ November 21, 2012

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LEILA P HANN  
11/21/2012



NDA 204307

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Cypress Pharmaceutical, Inc.  
2944 W. 143<sup>rd</sup> Ter  
Leawood, KS 66224

ATTENTION: Janet K. DeLeon, RAC  
Director of Product Development

Dear Ms. DeLeon

Please refer to your New Drug Application (NDA) dated April 23, 2012, received April 24, 2012, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Hydrocodone Bitartrate and Chlorpheniramine Maleate Oral Solution, 5 mg/4mg per 5 mL.

We also refer to your August 2, 2012, correspondence, received August 2, 2012, requesting review of your proposed proprietary name, Vituz. We have completed our review of the proposed proprietary name, Vituz, and have concluded that it is acceptable.

The proposed proprietary name, Vituz, 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 August 2, 2012, 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, Leila Hann, at (301) 796-3367.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh

Director

Division of Medication Error Prevention and Analysis

Office of Medication Error Prevention and Risk Management

Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

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/s/  
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CAROL A HOLQUIST  
10/26/2012



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**FACSIMILE TRANSMITTAL SHEET**

**DATE:** October 19, 2012

<b>To:</b> Janet DeLeon, Director of Product Development	<b>From:</b> Leila Hann Regulatory Management Officer
<b>Company:</b> Cypress Pharmaceutical	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Fax number:</b> 913-681-0669	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 913-681-0667	<b>Phone number:</b> 301-796-3367

**Subject:** NDA 204307 (Vituz) Carton and Container labeling

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

**Comments:**

**Document to be mailed:** YES xNO

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Your application is currently under review and we have the following comments regarding your carton and container labeling:

Revise the presentation of the proprietary name, "TRADENAME", from UPPERCASE to Title Case "Tradenname" to improve readability of the name. Words set in upper and lower case form recognizable shapes, making them easier to read than the rectangular shape that is formed by words set in all capital letters.

If you have any questions, please contact Leila Hann, Regulatory Program Manager, at 301-796-3367.

Drafted: L. Hann/ October 19, 2012  
Cleared: S. Barnes/ October 19, 2012  
Finalized: L. Hann/ October 19, 2012

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LEILA P HANN  
10/19/2012



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**FACSIMILE TRANSMITTAL SHEET**

**DATE:** October 11, 2012

<b>To:</b> Janet DeLeon, R.A..C.	Leila Hann
<b>Company:</b> Cypress Pharmaceutical, Inc.	<b>From:</b> Regulatory Management Officer
<b>Fax number:</b> 913-681-0669	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Phone number:</b> 913-681-0667	<b>Fax number:</b> 301-796-9728
	<b>Phone number:</b> 301-796-3367

**Subject:** NDA 204307 (Vituz) Information Request

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

**Comments:**

**Document to be mailed:** YES xNO

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Per federal regulation 21 CFR 314.50(d)(5)(vi)(b), submit a safety update for your proposed drug product. The safety update should include clinical studies, animal studies, if any, post marketing reports for the active ingredients, and safety information reported in literatures, covering the period from the initial NDA submission to the safety update. Submit the required safety update in 2 weeks.

Please provide a response by email or facsimile (301-796-9728), by 3:00PM Wednesday, October 25, 2012. Your response must also be submitted formally to the IND shortly thereafter. If you have any questions, please contact Leila P. Hann, Regulatory Project Manager, at 301-796-3367.

Drafted: X. Wang/ October 10, 2012  
T. Durmowicz/ October 10, 2012  
Cleared: S. Barnes/ October 11, 2012  
Finalized: L. Hann/ October 11, 2012

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/s/  
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LEILA P HANN  
10/11/2012

## Liu, Youbang

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**From:** Liu, Youbang  
**Sent:** Wednesday, August 01, 2012 2:36 PM  
**To:** 'jdeleon@cypressrx.com'  
**Cc:** Hann, Leila  
**Subject:** Information Request for NDA 204,307

Dear Ms. DeLeon:

We are reviewing the Chemistry, Manufacturing and Controls section of your submission for NDA 204,307 received April 24, 2012. We have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your submission:

- The antimicrobial effectiveness testing parameters do not comply with USP<51> as provided in Table 3.2.P.2.5-1, Section 3.2.P.2.5, pg. 2 of 3. The initial inoculum for Category 3 drug products should result in a test solution with a bacterial suspension between 10<sup>5</sup> and 10<sup>6</sup> cfu/ml. The data table indicates that the test solutions contained bacterial suspensions below this level.

Please acknowledge the receipt of this email and provide the time line of the amendment submission.

Regards,

Youbang Liu  
Regulatory Project Manager  
ONDQA/OPS/CDER/FDA  
Division III of New Drug Quality Assessment  
Phone: (301) 796-1926  
Fax: (301) 796-9748

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/s/  
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YOUBANG LIU  
08/01/2012



NDA 204307

**PROPRIETARY NAME REQUEST  
UNACCEPTABLE**

Cypress Pharmaceutical, Inc.  
2944 W 143<sup>rd</sup> Terrace  
Leawood, KS 66224

ATTENTION: Janet K. DeLeon, RAC  
Director of Product Development

Dear Ms. DeLeon:

Please refer to your New Drug Application (NDA) dated April 23, 2012, received April 24, 2012, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Hydrocodone Bitartrate and Chlorpheniramine Maleate Oral Solution, 5 mg/4 mg per 5 mL.

We also refer to your April 24, 2012, correspondence, received April 25, 2012, 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:



NDA 204307

We note that you have proposed an alternate proprietary name in your submission dated April 24, 2012. In order to initiate the review of the alternate proprietary name, Vituz, submit a new complete request for proprietary name review. 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 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, Leila Hann at (301) 796-3367.

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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CAROL A HOLQUIST  
07/24/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>CMC MICRO &amp; STERILITY ASSURANCE REVIEW REQUEST</b>		
TO (Division/Office): <b>New Drug Microbiology Staff</b>  <i>E-mail to: CDER OPS IO MICRO</i> <i>Paper mail to: WO Bldg 51, Room 4193</i>			FROM: Youbang Liu, Project Manager, ONDQA  PROJECT MANAGER (if other than sender):	
REQUEST DATE 7/6/12	IND NO.	NDA NO. 204307	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT 4/24/12
NAMES OF DRUG (b) (4) oral solution	PRIORITY CONSIDERATION		PDUFA DATE <b>2/24/13</b>	DESIRED COMPLETION DATE
NAME OF APPLICANT OR SPONSOR: <b>CYPRESS PHARMACEUTICAL INC</b>				
<b>GENERAL PROVISIONS IN APPLICATION</b>				
<input type="checkbox"/> 30-DAY SAFETY REVIEW NEEDED <input type="checkbox"/> CBE-0 SUPPLEMENT <input checked="" type="checkbox"/> NDA FILING REVIEW NEEDED BY: <u>10/14/2012</u> <input type="checkbox"/> CBE-30 SUPPLEMENT <input type="checkbox"/> BUNDLED <input type="checkbox"/> CHANGE IN DOSAGE, STRENGTH / POTENCY <input type="checkbox"/> DOCUMENT IN EDR				
<b>COMMENTS / SPECIAL INSTRUCTIONS:</b> Please review Comments 1 & 2 in the attached 74 day letter. Please also review the applicant responses when they are available.				
SIGNATURE OF REQUESTER  Youbang Liu			REVIEW REQUEST DELIVERED BY (Check one): <input checked="" type="checkbox"/> DARRTS <input type="checkbox"/> EDR <input checked="" type="checkbox"/> E-MAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND	
			DOCUMENTS FOR REVIEW DELIVERED BY (Check one): <input type="checkbox"/> EDR <input checked="" type="checkbox"/> E-MAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND	



NDA 204307

**FILING COMMUNICATION**

Cypress Pharmaceutical, Inc.  
2944 W. 143<sup>rd</sup> Terrace  
Leawood, Kansas 66224

Attention: Janet K. DeLeon, R.A.C.  
Director of Product Development

Dear Ms. DeLeon:

Please refer to your New Drug Application (NDA) dated April 23, 2012, received April 24, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for (b) (4) (hydrocodone bitartrate and chlorpheniramine maleate) oral solution at 5 mg hydrocodone bitartrate and 4 mg chlorpheniramine maleate per 5 mL.

We have completed our filing review and have determined that your application is 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 February 22, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by November 7, 2012.

We request that you submit the following information:

1. Provide test methods and acceptance criteria to demonstrate the product is free of the objectionable microorganisms of the Burkholderia cepacia complex. We recommend that potential sources are examined and sampled as process controls, and these may include raw materials and the manufacturing environment.  
A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria. Your test method should be

validated and a discussion of those methods should be provided. Test methods validation should address multiple strains of the species and cells that are acclimated to the environments (e.g., warm or cold water) that may be tested.

2. This pertains to the antimicrobial effectiveness and microbial limits tests which are referenced to USP (USP general chapters 51, 61 and 62). Provide a description of the actual procedures used as well as the results of method verification studies as appropriate.
3. There is an insufficient amount of stability (6 months) for the proposed 2 year expiry for the drug product. Provide sufficient stability data to support the proposed drug product expiry period, or shorten the expiry period appropriately.
4. Provide a complete list of regulatory drug product specifications.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. For drug products other than vaccines, the verbatim **bolded** statement must be present: **“To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch”**. Generic manufacturer’s websites are unacceptable. Change (b) (4) to “at”.
2. **Bolded** revision date (i.e., **“Revised: MM/YYYY or Month Year”**) must be at the end of HL. Remove brackets.
3. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*]. FPI 1.2, change (b) (4) to [*see Use in Specific Populations (8.4)*].

We request that you resubmit labeling that addresses these issues by July 27, 2012. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for 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.

### **PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form

with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full deferral request is denied.

If you have any questions, call Leila P. Hann, Regulatory Project Manager, at (301) 796-3367.

Sincerely,

*{See appended electronic signature page}*

Lydia I. Gilbert-McClain, M.D., F.C.C.P.  
Deputy Director  
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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LYDIA I GILBERT MCCLAIN  
07/06/2012



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/s/  
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LEILA P HANN  
06/15/2012

**REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW  
CONSULTATION**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

**\*\*Please send immediately following the Filing/Planning meeting\*\***

TO: <b>CDER-DDMAC-RPM</b>	FROM: (Name/Title, Office/Division/Phone number of requestor) <b>Leila Hann/Regulatory Project Manager, ODEII/DPARP/6-3367</b>
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REQUEST DATE <b>June 15, 2012</b>	IND NO.	NDA/BLA NO. <b>NDA 204307</b>	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
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NAME OF DRUG <b>hydrocodone bitartrate and chlorpheniramine maleate</b>	PRIORITY CONSIDERATION <b>Standard</b>	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) <b>October 24, 2012</b>
--	---	------------------------	---

NAME OF FIRM: <b>Cypress Pharmaceuticals</b>	PDUFA Date: <b>February 22, 2013 (Goal: December 5, 2012)</b>
---	---

**TYPE OF LABEL TO REVIEW**

<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 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 type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION
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**EDR link to submission:**  
<\\cdsesub1\EVSPROD\NDA204307\0000>

**Please Note:** There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

**COMMENTS/SPECIAL INSTRUCTIONS:**  
 Filing/Planning Meeting: June 8, 2012  
 Mid-Cycle Meeting: N/A  
 Labeling Meetings: September 25, 2012 (planned but may not be needed)  
 Wrap-Up Meeting: October 1, 2012  
 PDUFA Date: February 22, 2013      Division Goal Date: December 5, 2012

Cypress submitted a new NDA dated, April 24, 2012 for hydrocodone bitartrate and chlorpheniramine maleate for the relief of cough due to common cold and relief of symptoms related to upper respiratory allergies. Please review the following contained in the submission: PI and carton and container.

SIGNATURE OF REQUESTER: **Leila Hann**

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> eMAIL <input type="checkbox"/> HAND
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/s/  
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LEILA P HANN  
06/15/2012

## REQUEST FOR CONSULTATION

TO (Office/Division): **Controlled Substance Staff**

FROM (Name, Office/Division, and Phone Number of Requestor):  
**Leila P. Hann, ODEII/DPARP, 301-796-3367**

DATE  
**May 09, 2012**

IND NO.

NDA NO.  
**204307**

TYPE OF DOCUMENT  
**Original Submission**

DATE OF DOCUMENT  
**April 24, 2012**

NAME OF DRUG  
**hydrocodone bitartrate/  
chlorpheniramine maleate**

PRIORITY CONSIDERATION  
**standard**

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE  
**October 22, 2012**

NAME OF FIRM: **Cypress Pharmaceutical, Inc.**

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** This is a consult request for your attendance and input at the planning-filing, mid-cycle, and wrap-up meetings for this application. PDUFA Date: February 22, 2013

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)

- DFS       EMAIL       MAIL       HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/  
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LEILA P HANN  
05/10/2012



NDA 204307

**NDA ACKNOWLEDGMENT**

Cypress Pharmaceutical, Inc.  
2944 W. 143<sup>rd</sup> Terrace  
Leawood, Kansas 66224

Attention: Janet K. DeLeon, R.A.C.  
Director of Product Development

Dear Ms. DeLeon:

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: Zutripro (hydrocodone bitartrate/chlorpheniramine maleate) solution  
5mg per ml and 4mg per ml

Date of Application: April 23, 2012

Date of Receipt: April 24, 2012

Our Reference Number: NDA 204307

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 June 22, 2012, 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/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. 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.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

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, Allergy, and Rheumatology 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/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call Leila P. Hann, Regulatory Project Manager, at (301) 796-3367.

Sincerely,

*{See appended electronic signature page}*

Leila P. Hann  
Regulatory Project Manager  
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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LEILA P HANN  
05/08/2012