

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022424Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22242

SUPPL #

HFD #

Trade Name: Flowtuss

Generic Name: Hydrocodone and Guaifenesin Oral Solution

Applicant Name: Mikart, Inc.

Approval Date, If Known May14, 2015

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 primary assessment of this submission pertained to the evaluation of the pharmacokinetic characteristics of hydrocodone and guaifenesin after administration of the proposed product compared to a reference. Apart from the pharmacokinetic information and safety information from the BE study, no additional efficacy and safety information was obtained.

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?

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# 205474 Obredon®

NDA# 19-111 Tussionex®

NDA# 22-439 Zutripro®

NDA# 22-4420 Rezira®

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:

Name of person completing form: Laura Musse
Title: Regulatory Health Project Manager
Date: May XX, 2015

OND/DPARP Deputy Director signing form: Lydia Gilbert-McClain, M.D.
Title: Deputy Director

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

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

/s/

LAURA MUSSE
05/14/2015

LYDIA I GILBERT MCCLAIN
05/14/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 22424 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Flowtuss Established/Proper Name: Hydrocodone Bitartrate & Guaifenesin Dosage Form: Oral Solution		Applicant: Mikart Inc Agent for Applicant (if applicable):
RPM: Laura Musse		Division: Pulmonary, Allergy, and Rheumatology Products
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) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)	<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: May 14, 2015</p> <p><i>Note: 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.</i></p>	
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is _____ 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		<input checked="" type="checkbox"/> Complete Response- September 28, 2011
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(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).

³ 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.

Review priority: Standard Priority
 Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

- | | |
|---|---|
| <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 |
| <input type="checkbox"/> Breakthrough Therapy designation | |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ 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 checked="" type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
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 checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s) May 14, 2015 CR-September 28, 2011
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ 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>	<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"> Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input checked="" type="checkbox"/> May 1, 2015
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input checked="" type="checkbox"/> November 29, 2010
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> Most-recent draft labeling 	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
<ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> Review(s) <i>(indicate date(s))</i> 	Acceptability Letter-March 13, 2015 Acceptability Review-March 5, and 9, 2015 Conditional Acceptability Letter and review--August 9, 2011
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input type="checkbox"/> DMEPA: <input checked="" type="checkbox"/> March 5, 2015 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> None OPDP: <input checked="" type="checkbox"/> April 28, 2015 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> 505(b)(2) March 31, 2015 August 31, 2011
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo <i>(indicate date)</i> If yes, OC clearance for approval <i>(indicate date of clearance communication)</i> 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC If PeRC review not necessary, explain: 	April 29, 2015
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	May 15, 13, 1, April 21, March 16, February 5, January 30, and 7, 2015, August 8, April 28 and 5, February 11, 2011, December 27 and 13, 2010
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/>
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/>
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input type="checkbox"/>
<ul style="list-style-type: none"> Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	
Decisional and Summary Memos	
❖ 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>)(<i>Deputy Director</i>)	<input checked="" type="checkbox"/> May 15, 2015 September 28, 2011
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> April 29, 2015 September 8, 2011
PMR/PMC Development Templates (<i>indicate total number</i>) (2)-pending	<input checked="" type="checkbox"/> None
Clinical	
❖ Clinical Reviews	
<ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	<input type="checkbox"/>
<ul style="list-style-type: none"> Clinical review(s) (<i>indicate date for each review</i>) 	April 24, 2015, August 18, 2011, February 9, 2011
<ul style="list-style-type: none"> 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>)	June 8, and April 22, 2010
❖ Clinical reviews from immunology and 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>)	<input checked="" type="checkbox"/> N/A

❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<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
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/>
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/>
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> February 2, 2011
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> April 24, 2015, August 23, January 28, 2011
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> February 4, 2015, January 11, 2011
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> May 1, 2015, August 31, 2011
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> April 23, 2015, July 21 and January 20, 2011
❖ 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
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input type="checkbox"/>

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> April 24, 2015, December 8, 2014, August 26, April 27 and January 11, 2011
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> August 16, 2011 December 8, 2014
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ 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>	August 27, 2011, page 58
<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 or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i>	Date completed: February 12, 2015 July 22, and January 3, 2011 <input checked="" type="checkbox"/> Acceptable- recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) <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 checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁵ 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.

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input checked="" type="checkbox"/> Done
❖ For Breakthrough Therapy(BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done (<i>Send email to CDER OND IO</i>)
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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

/s/

LAURA MUSSE
05/14/2015

PeRC Meeting Minutes
April 29, 2015

PeRC Members Attending:

Lynne Yao (Chair for all products (Non Responsive)
Robert "Skip" Nelson
Wiley Chambers
Rosemary Addy
George Greeley
Frede Crooner
Tom Smith
Karen Davis-Bruno
Daiva Shetty
Andrew Mulberg (Non Responsive
Greg Reaman (Did not review (Non Responsive)
Barbara Buch
Adrienne Hornatko-Munoz
Barbara Buch
Andrew Mosholder (Non Responsive
Hari Cheryl Sachs
Julia Pinto
Lily Mulugeta
Olivia Ziolkowski
Kevin Krudys
Rachel Witten
Dianne Murphy
Maura O'Leary
Kristiana Brugger (Did not review (Non Responsive)

Agenda

9:00	NDA	Non Responsive	
9:40	NDA		
9:50	IND		
10:10	IND		
10:30	IND		
10:50	NDA		
11:00	NDA		
11:10	BLA		
11:20	NDA		
11:30	NDA	22279 & 22424	Hycofesin (hydrocodone/guaifenesin/pseudoephedrine) Hydrocodone and Guaifenesin (Partial Waiver/Assessment)
			(b) (4)
11:40	BLA	Non Responsive	
11:50	IND		
	<i>IND</i>		

4 Page(s) has been Withheld in Full as Non Responsive

Non Responsive

Hycofesin & Hydrocodone and Guifenesin (Partial Waiver/Assessment)

- Proposed Indication: (b) (4)

- The Division is requesting a partial waiver of studies for both products in children less than 6 year of age due to safety since hydrocodone is contraindicated in this age group due to the increased risk for fatal respiratory depression. The Division is requesting a deferral of studies in children 6 years and older because adult studies are complete and ready for approval. The plan for pediatric studies includes an evaluation of PK and safety.
- PeRC Recommendations:
 - The PeRC agreed with the plan for a partial waiver (based on safety) and deferral of pediatric studies.
 - The PeRC also recommends that the sponsor advance the timeline for completion of pediatric studies.

Non Responsive

2 Page(s) has been Withheld in Full as Non Responsive

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/s/

GEORGE E GREELEY
05/14/2015



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

FACSIMILE TRANSMITTAL SHEET

DATE: May13, 2015

To: Jason Waldroup Director, Regulatory Affairs	From: Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
Company: Mikart Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: (404) 352-0351	Fax number: (301) 796-9728
Phone number: (404) 351-4510	Phone number: (240) 402-3720
Subject: NDA 22424- Flowtuss, (hydrocodone and guaifenesin)-and NDA 22279-Hycofenix (hydrocodone/guaifenesin/pseudoephedrine -Label information request.	

Total no. of pages including cover: 22

Comments:

Document to be mailed: YES X- NO

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NDA 22424
NDA 22279

Your NDA submissions dated, November 18, 2014 to NDA 22424 and December 4, 2014 to NDA 22279 are currently under review. The Division's proposed insertions are underlined; deletions are in strike-outs. These comments are not all-inclusive and we may have additional comments as we continue our review. We have the following comments and requests for information:

1. Review and accept the required changes to the Highlight section for both the Flowtuss and Hycofenix labels and the corrections and edits to section 12.3 which are in Tracked
2. Change format in the Label attachments. The following are your questions from your e-mail correspondence dated May 11, 2015 and our responses:

For item #2, we have several comments/questions:

Mikart intends to use lower case lettering for the established name in accordance with current Agency guidance.

- *Should a similar change be made for the 22-279 product (e.g., Hycofenix (hydrocodone bitartrate, pseudoephedrine hydrochloride and guaifenesin) Oral Solution?*
- *This comment indicates the change is to be made on the package insert, however earlier Agency comment requested (b) (4) in sections 11 and 16. Is it in these two sections that the Agency is requesting that the established name be added?*

FDA Response:

- Use of lower case is acceptable. This should also be reflected in the Hycofenix label.
- With regard to the inclusion of “oral solution”, the IR may have been confusing or incorrect. For the package insert “oral solution” should be included in the Highlight section (see tracked changes), and in the first sentences of sections 11 and 16 only (where they are already correctly placed).

For item #3, can we move

(b) (4)

FDA Response:

- No, the (b) (4) statement should not be in any labeling including anywhere on the carton and container. Product labels donot include what is not in the product in the labeling.

Respond to these Information Requests by email (Laura.Musse@fda.hhs.gov) or facsimile (301-796-9728), by Thursday, May 14, 2015. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Laura Musse, Regulatory Health Project Manager, at 240-402-3720.

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

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/s/

LAURA MUSSE
05/13/2015



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

FACSIMILE TRANSMITTAL SHEET

DATE: May 8, 2015

To: Jason Waldroup Director, Regulatory Affairs	From: Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
Company: Mikart Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: (404) 352-0351	Fax number: (301) 796-9728
Phone number: (404) 351-4510	Phone number: (240) 402-3720
Subject: NDA 22424- Flowtuss, (hydrocodone and guaifenesin)-and NDA 22279-Hycofenix (hydrocodone/guaifenesin/pseudoephedrine -Label information request.	

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES X- NO

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NDA 22424
NDA 22279

Your NDA submissions dated, November 18, 2014 to NDA 22424 and December 4, 2014 to NDA 22279 are currently under review. These comments are not all-inclusive and we may have additional comments as we continue our review. We have the following comments and requests for information:

1. There is an error in the Flowtuss PI.doc. Under section 12.3 Pharmacokinetics, it states that “the geometric mean C_{max} and AUC_{0-inf} for guaifenesin were 2.0 mcg/mL and 26 mcg·hr/mL”. The correct sentence should read “the geometric mean C_{max} and AUC_{0-inf} for guaifenesin were 2.0 mcg/mL and 2.6 mcg·hr/mL”. Insert the missing decimal point as follows: 2.6
2. The name should appear as follows: Flowtuss (Hydrocodone Bitartrate and Guafensin) Oral Solution. This change must be made on all container and carton labels, as well as the Package insert.
3. Remove the (b) (4) statement from the container/carton labels. This comment is also relevant to the container/carton labeling for NDA 22279.

Respond to these Information Requests by email (Laura.Musse@fda.hhs.gov) or facsimile (301-796-9728), by Tuesday, May 12, 2015. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Laura Musse, Regulatory Health Project Manager, at 240-402-3720.

Review/History Clearance From

(To be used/added as a third page to faxed, electronic, or other correspondence, where applicable)

Initiated by:	YRen JPinto Durmowicz	Date: 5/8/15
Drafted by:	LMusse	Date: 5/8/15
Clearance:	SBarnes	Date: 5/8/15
Finalized:	LMusse	Date: 5/8/15
File Name:	Labeling IR Round 3	Date: 5/8/15

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/s/

LAURA MUSSE
05/08/2015



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

FACSIMILE TRANSMITTAL SHEET

DATE: May 1, 2015

To: Jason Waldroup Director, Regulatory Affairs	From: Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
Company: Mikart Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: (404) 352-0351	Fax number: (301) 796-9728
Phone number: (404) 351-4510	Phone number: (240) 402-3720
Subject: NDA 22424- Flowtuss, (hydrocodone and guaifenesin)- Label information request.	

Total no. of pages including cover: 12

Comments:

Document to be mailed: YES X- NO

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NDA 22424

Your NDA submission dated, November 18, 2014 to NDA 22424 is currently under review. The enclosed label contains the Division's edits to your draft package insert (PI) and carton and container submitted on April 28, 2015. The Division's proposed insertions are underlined; deletions are in strike-outs. These comments are not all-inclusive and we may have additional comments as we continue our review. We also have the following comments and request for information:

Recently, FDA has begun a formal review of label formatting in an attempt to comply with official labeling format and foster consistency in labeling. As a result, you will note that there are several format and naming alterations that are different from those found in similar products already on the market. These labels will undergo a similar label format review when new label supplements are received.

Carton and Container

1. The established names should be presented in a manner consistent with 21 CFR 201.10(g)(2) which requires that the established name be at least half the size of the letters comprising the proprietary name and have a prominence consistent with the proprietary name in terms of type, size, color, and font.
2. Delete the text (b) (4)

Respond to these Information Requests by email (Laura.Musse@fda.hhs.gov) or facsimile (301-796-9728), by Thursday, May 7, 2015. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Laura Musse, Regulatory Health Project Manager, at 240-402-3720.

Review/History Clearance From

(To be used/added as a third page to faxed, electronic, or other correspondence, where applicable)

Initiated by:	ADurmowicz AShaw	Date: 5/1/15
Drafted by:	LMusse	Date: 5/1/15
Clearance:	SBarnes	Date: 5/1/15
Finalized:	LMusse	Date: 5/1/15
File Name:	Labeling IR Round 2	Date: 5/1/15

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/s/

LAURA MUSSE
05/01/2015



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

FACSIMILE TRANSMITTAL SHEET

DATE: April 21, 2015

To: Jason Waldroup Director, Regulatory Affairs	From: Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
Company: Mikart Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: (404) 352-0351	Fax number: (301) 796-9728
Phone number: (404) 351-4510	Phone number: (240) 402-3720
Subject: NDA 22424- Flowtuss, (hydrocodone and guaifenesin)- Label information request.	

Total no. of pages including cover: 12

Comments:

Document to be mailed: YES X- NO

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NDA 22424

Your NDA submission dated, November 18, 2014 to NDA 22424 is currently under review. The enclosed label contains the Division's edits to your propose package insert (PI) and carton and container. The Division's proposed insertions are underlined; deletions are in strike-outs. These comments are not all-inclusive and we may have additional comments as we continue our review. We also have the following comments:

1. In your drug label, section 12.3 Pharmacokinetics; (b) (4)
[REDACTED]
[REDACTED] Please update those values with those obtained from your own studies (i.e., study 110028 and study 11467601).
2. Revise the presentation of the proprietary name from all caps (i.e. FLOWTUSS) to title case (i.e. Flowtuss) to improve readability of the name. Words set in title case are easier to read than the rectangular shape that is formed by words set in all capital letters.

Respond to these Information Requests by email (Laura.Musse@fda.hhs.gov) or facsimile (301-796-9728), by Friday, April 24, 2015. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Laura Musse, Regulatory Health Project Manager, at 240-402-3720.

Review/History Clearance From

Drafted by:	LMusse	Date: 4/17/15
Clearance:	SBarnes	Date: 4/17/15
	XWang	Date: 4/17/15
	ADurmowicz	Date: 4/21/15
	YRen	Date: 4/17/15
	SDoddapaneni	Date: 4/20/15
Finalized:	LMusse	Date: 4/21/15
File Name:	Labeling IR	Date: 4/21/15

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/s/

LAURA MUSSE
04/21/2015



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

FACSIMILE TRANSMITTAL SHEET

DATE: March 16, 2015

To: Jason Waldroup Director, Regulatory Affairs	From: Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
Company: Mikart Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: (404) 352-0351	Fax number: (301) 796-9728
Phone number: (404) 351-4510	Phone number: (240) 402-3720
Subject: NDA 22279-(Hydrocodone/Guaifenesin/Pseudoephedrine) and NDA 22424- (Hydrocodone and Guaifenesin)-Post Marketing Requirements information request.	

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES X- NO

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Your resubmissions dated December 4, 2014, to NDA 22279, and November 18, 2014, to NDA 22424 are currently under review. We have the following comments and requests for information:

Attached are our current general requirements for the pediatric post marketing requirements (PMR) studies for the opioid-containing combination cough and cold products.

We note you have submitted a request for a waiver for patients less than 6 years of age. We request your agreement to conduct the following studies and completion of milestone timelines.

PREA Post Marketing Requirement (PMR)

1. A single-dose pharmacokinetic study whose primary objective is to identify the dose(s) of INSERT PRODUCT that result in exposures of INSERT DRUG COMPONENTS in children (aged 6 to 11) and adolescents (aged 12 to 17 years) that are similar to the exposures seen in adults at the recommended dose. The population eligible for enrollment should be otherwise healthy children and adolescents with cough/cold symptoms for whom a combination product that includes an opioid antitussive would be an appropriate symptomatic treatment.

PMR Scheduled Milestones:

Final Protocol Submission:

Trial Completion:

Final Report Submission:

2. An open-label multi-dose safety and tolerability study at the dose(s) that result in drug exposures in children (aged 6 to 11) and adolescents (aged 12 to 17 years) that are similar to the exposures seen in adults at the recommended dose. The population eligible for the study would be children and adolescents with cough/cold symptoms for whom a combination product that includes an opioid antitussive would be an appropriate symptomatic treatment. The study will enroll a total of approximately 400 children aged 6 to 17 inclusive in two cohorts (6-11 years, 12 to 17 years).

PMR Scheduled Milestones:

Final Protocol Submission:

Trial Completion:

Final Report Submission:

Respond to these Information Requests by email (Laura.Musse@fda.hhs.gov) or facsimile (301-796-9728), by Friday, March 20, 2015. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Laura Musse, Regulatory Health Project Manager, at 240-402-3720.

Attachment

General Cough and Cold Combination Product PREA Requirements

Below are our current general requirements for pediatric PMR studies for opioid-containing combination cough and cold products. The requirements could change in the future based on changes in regulatory policy.

Waivers and Deferrals

- a. Waiver for pediatric patients less than 6 years of age based on evidence the product would be unsafe or ineffective
- b. Deferral for pediatric patients 6-17 years of age until drug product is approved for the adult population.

Pediatric Studies

- A single-dose pharmacokinetic study whose primary objective is to identify the dose(s) of INSERT PRODUCT that result in exposures of INSERT DRUG COMPONENTS in children (aged 6 to 11) and adolescents (aged 12 to 17 years) that are similar to the exposures seen in adults at the recommended dose. The population eligible for enrollment should be otherwise healthy children and adolescents with cough/cold symptoms for whom a combination product that includes an opioid antitussive would be an appropriate symptomatic treatment.
- An open-label multi-dose safety and tolerability study at the dose(s) that result in drug exposures in children (aged 6 to 11) and adolescents (aged 12 to 17 years) that are similar to the exposures seen in adults at the recommended dose. The population eligible for the study would be children and adolescents with cough/cold symptoms for whom a combination product that includes an opioid antitussive would be an appropriate symptomatic treatment. The study will enroll a total of approximately 400 children aged 6 to 17 inclusive in two cohorts (6-11 years, 12 to 17 years).

Timelines

In general, the submission of the single-dose PK study report should take no longer than 2-3 years from the start. The submission of the safety study report should take no longer than about 3-4 years from the start.

Review/History Clearance From

Initiated by:	ADurmowicz	Date: 3/12/15
Drafted by:	LMusse	Date: 3/16/15
Clearance:	SBarnes	Date: 3/16/15
Finalized:	LMusse	Date: 3/16/15
File Name:	PREA PMR IR	

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/s/

LAURA MUSSE
03/16/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022424

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Mikart, Inc.
1750 Chattahoochee Avenue, NW
Atlanta, GA 30318

ATTENTION: Jason Waldroup
Director, Regulatory Affairs

Dear Mr. Waldroup:

Please refer to your New Drug Application (NDA) submitted under 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Hydrocodone Bitartrate and Guaifenesin Oral Solution, 2.5 mg/200 mg per 5 mL.

We also refer to:

- Your correspondence, dated and received December 12, 2014, requesting review of your proposed proprietary name, Flowtuss
- Your amendment to the Request for Proprietary Name Review, dated and received January 13, 2015.

We have completed our review of the proposed proprietary name, Flowtuss and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your December 12, 2014 and January 13, 2015, submissions are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

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 Laura Musse, Regulatory Project Manager in the Office of New Drugs, at (240) 402-3720.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy 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/

TODD D BRIDGES
03/13/2015



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

FACSIMILE TRANSMITTAL SHEET

DATE: February 5, 2015

To: Jason Waldroup Director, Regulatory Affairs	From: Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
Company: Mikart Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: (404) 352-0351	Fax number: (301) 796-9728
Phone number: (404) 351-4510	Phone number: (240) 402-3720
Subject: NDA 022279-(Hydrocodone/Guaifenesin/Pseudoephedrine) and NDA 022424- (Hydrocodone and Guaifenesin) Information Request	

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES X- NO

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Your resubmissions dated December 4, 2014, to NDA 022279, and November 18, 2014, to NDA 022424 is currently under review. We have the following requests for information:

1. Submit revised labeling assuring that the labeling structure format and language conforms to the Physician Labeling Rule (PLR) Requirements for Prescribing Information including format labeling tools and checklist, available at: <http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/lawsactsandrules/ucm084159.htm>
2. Refer to the labels of recently approved combination cough and cold medications for guidance.

Respond to these Information Requests by email (Laura.Musse@fda.hhs.gov) or facsimile (301-796-9728), by Friday, February 20, 2015. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Laura Musse, Regulatory Health Project Manager, at 240-402-3720.

Review/History Clearance From

Initiated by:	XWang	Date:	2/5/15
Drafted by:	LMusse	Date:	2/5/15
Clearance:	SBarnes	Date:	2/5/15
Finalized:	LMusse	Date:	2/5/15
File Name:	Label PLR format Request		

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/s/

LAURA MUSSE
02/05/2015

NDA022424



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

FACSIMILE TRANSMITTAL SHEET

DATE: January 30, 2015

To: Jason Waldroup	From: Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
Company: Mikart, Inc	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: (404) 352-0351	Fax number: (301) 796-9728
Phone number: (404) 351-4510	Phone number: (240) 402-3720
Subject: NDA 022424- (Hydrocodone and Guaifenesin) Information Request	

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES X- NO

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Your resubmission dated November 18, 2014, to NDA 022424, is currently under review. We have the following comment and requests for information:

Submit revised labeling structure and language to be consistent with the labels of the approved hydrocodone and hydrocodone-guaifenesin products, including but not are limited to the following sections: Dosage and Administration, Drug Interactions, Warnings and Precautions, Clinical Pharmacology.

Please provide a response to the requests by email (Laura.Musse@fda.hhs.gov) or facsimile (301-796-9728), by 12 noon on Monday, February 9, 2015. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Laura Musse, Regulatory Project Manager, at 240-402-3720.

Initiated by:	CP	1/26/15
Cleared by:	SBarnes	1/29/15
	Brar/Ren	1/30/15
Finalized:	LMusse	1/30/15
File Name:	CP IR # 1	1/30/15

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/s/

LAURA MUSSE
01/30/2015



NDA 22424

**ACKNOWLEDGE –
CLASS 2 RESUBMISSION**

Mikart, Inc.
1750 Chattahoochee Avenue, NW.
Atlanta, GA 30318

Attention: Jason Waldroup
Director, Regulatory Affairs

Dear Mr. Waldroup:

We acknowledge receipt on November 18, 2014 of your November 5, 2014, resubmission to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for hydrocodone and guaifenesin oral solution, 2.5 mg/200 mg per 5 milliliters.

We consider this a complete, class 2 response to our September 28, 2011 action letter. Therefore, the user fee goal date is May18, 2015.

If you have any questions, call me, at (240) 402-3720.

Sincerely,

{See appended electronic signature page}

Laura Musse, R.N., M.S., C.R.N.P.
Regulatory Health 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/

LAURA MUSSE
01/07/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 22-424 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Flowtuss Established/Proper Name: hydrocodone/guaifenesin Dosage Form: oral solution		Applicant: Tiber Laboratories, LLC Agent for Applicant (if applicable): Mikart
RPM: Sadaf Nabavian, Pharm.D.		Division: Pulmonary, Allergy, and Rheumatology Products
<p>NDA: 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>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)): NDA 5-213 Hycodan</p> <p>Provide a brief explanation of how this product is different from the listed drug. The proposed product does not contain homatropine mehtylbromide and instead contains guaifenesin</p> <p>If no listed drug, explain. <input checked="" type="checkbox"/> This application relies on literature. <input checked="" type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p><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></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>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.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>September 29, 2011</u>; Action Date <u>September 28, 2011</u> 		<input type="checkbox"/> AP <input type="checkbox"/> TA <input checked="" type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input type="checkbox"/> None

¹ 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.

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics²</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p> <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 </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> <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> 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> REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> REMS not required </p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> 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

² 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"> Is approval of this application blocked by any type of exclusivity? 	<input type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> 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> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (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> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (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> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (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> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> 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> 	<input 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"> 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. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<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 ³	September 19, 2011
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: 09/28/2011
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	11/29/2010
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

³ Fill in blanks with dates of reviews, letters, etc.
Version: 8/25/10

❖ 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>)	<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"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	11/29/2010
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> • Most-recent draft labeling 	02/23/2011
❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	Acceptable: 08/09/2011 Review: 8/09/2011
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input checked="" type="checkbox"/> RPM 01.31.2011 <input type="checkbox"/> DMEPA <input type="checkbox"/> DRISK <input type="checkbox"/> DDMAC <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	RPM Filing Review: 01.10.2011; 505(b)(2) Clearance: 08.31.2011
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	<input type="checkbox"/> Not a (b)(2)
❖ NDAs (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)	<input type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>N/A</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input 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>)	Deficiencies Preclude Discussion: 08.08.2011, Preclinical IR:

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
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	04.05.2011, Discipline Review Letter: 04.28.2011; CMC IR: 12.27.2010; NDA Acknowledgment: 12.13.2011
❖ Internal memoranda, telecons, etc.	Tcon: 05.05.2011
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" 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>)	PIND 76365 :04.11.2007
❖ 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>)	
Decisional and Summary Memos	
❖ 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 09.28.2011 (By Deputy Director)
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 09.08.2011
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	08.18.2011; See concurrence on the clinical reviews
• Clinical review(s) (<i>indicate date for each review</i>)	02.09.2011; 08.18.2011
• 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>)	06.08.2010 (Refer to MO's Review Section 4.6, Page 15)
❖ Clinical reviews from immunology and 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>)	<input checked="" type="checkbox"/> 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>)	<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

⁵ Filing reviews should be filed with the discipline reviews.
Version: 8/25/10

Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None See concurrence on stat review
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None 02.02.2011
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None See concurrence on CP Review
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 01.28.2011;08.23.2011
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> None 08.31.2011
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 07.21.2011; 01.20.2011
❖ 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
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None See concurrence with CMC Review
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	<input type="checkbox"/> None 08.26.2011
❖ Microbiology Reviews	<input type="checkbox"/> Not needed 08.16.2011
<input checked="" 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

❖ 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>)	Acceptable: CMC Review page 7 of 35, EA accepted on 03/17/2011
<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 sites⁶</i>)	Date completed: 08.10.2011 <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 checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁶ 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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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.

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

/s/

SADAF NABAVIAN
09/29/2011



NDA 022424

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Tiber Laboratories, LLC
5400 Laurel Springs Parkway, Suite 803
Suwanee, Georgia 30024

ATTENTION: Cassie Vitolo, RAC
Director, Regulatory Affairs

Dear Ms. Vitolo:

Please refer to your New Drug Application (NDA) dated November 29, 2010, received November 29, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hydrocodone Bitartrate and Guaifenesin Oral Solution, 2.5 mg and 200 mg per 5 mL.

We also refer to your May 13, 2011, correspondence, received May 16, 2011, requesting review of your proposed proprietary name, Flowtuss. We have completed our review of the proposed proprietary name, Flowtuss and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your May 13, 2011, 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, Sadaf Nabavian at (301) 796-2777.

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

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/s/

CAROL A HOLQUIST
08/09/2011



NDA 22-424

DEFICIENCIES PRECLUDE DISCUSSION

Tiber Laboratories, LLC
5400 Laurel Springs Parkway
Suite 803
Suwanee, GA 30024

Attention: Cassie Vitolo
Director, Regulatory Affairs

Dear Ms. Vitolo:

Please refer to your November 29, 2010, New Drug Application (NDA) submitted under section 505(b) of the Food, Drug, and Cosmetic Act for hydrocodone/guaifenesin.

We also refer to our February 11, 2011, letter in which we notified you of our target date of September 08, 2011, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals And Procedures – Fiscal Years 2008 Through 2012."

As part of our ongoing review of your application, we have identified deficiencies that preclude discussion of labeling and postmarketing requirements/commitments at this time.

This notification does not reflect a final decision on the information under review.

If you have any questions, call Sadaf Nabavian, Regulatory Project Manager, at (301) 796-2777.

Sincerely,

{See appended electronic signature page}

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

APPEARS THIS WAY ON ORIGINAL



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/s/

ANTHONY G DURMOWICZ
08/08/2011



NDA 22-424

DISCIPLINE REVIEW LETTER

Tiber Laboratories, LLC
Attention: Cassie Vitolo
Director, Regulatory Affairs
5400 Laurel Springs Parkway, Suite 803
Suwanee, GA 30024

Dear Ms. Vitolo:

Please refer to your New Drug Application (NDA) dated November 24, 2010, received November 29, 2010, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for hydrocodone bitartrate and guaifenesin oral solution.

We also refer to your submission dated January 6, 2011.

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

1. The guaifenesin drug substance impurity limits that you transcribed from guaifenesin USP monograph do not incorporate (b) (4) this is misleading. Amend your impurity analysis method to include (b) (4) in the impurity result calculation. Also update the guaifenesin drug substance specification table with the corrected drug substance impurity specifications, which are also modified in consideration of ICH Q3A.
2. The guaifenesin drug substance specifications for other individual impurities do not meet ICH Q3A requirements. Tighten the specification limits by considering both ICH Q3A recommendations and test results.
3. Drug product manufacturing process related comments are listed below.
 - a) (b) (4)
 - b) (b) (4)
Clarify this hold duration time limit in the manufacturing process section and master batch record.

- c) Provide product stability and microbial limit data to support your maximum product solution hold duration.
4. Provide the (b) (4) release testing requirements for all excipients. At least an identification test is required if the excipient is accepted on the basis of a Certificate of Analysis and is used within its retest period.
5. Drug product release and stability specifications related comments are listed below.
 - a) The specifications table has acceptance criteria for pseudoephedrine, which is not a component of this product. Update the specification table to remove the entry.
 - b) There is only one identification test for each drug substance. Include a complementary identification test.
 - c) Add a deliverable volume test to the product at 4 oz package configuration. USP <698> requires this test when the product is labeled to contain not more than 250 mL.
 - d) The drug product impurity acceptance criteria should follow ICH Q3B. At the proposed total daily dose for both hydrocodone and guaifenesin, impurities not less than (b) (4)% should be identified, impurities not less than (b) (4)% should be qualified. The acceptance criteria of NMT (b) (4)% for any other individual impurity is not acceptable if there are unidentified impurities in this category. We recommend you to segregate the identified and unidentified impurities and establish the corresponding acceptance criteria in reference to ICH Q3B. Impurities in the drug product not less than (b) (4)% should be qualified.
 - e) The total combined molds and yeasts count acceptance criterion of NMT (b) (4) CFU for the drug product is (b) (4) the USP <1111> recommended limit of NMT 20 cfu/g or mL for aqueous oral solution. Tighten the limit.
 - f) Conduct forced degradation studies of the drug product to identify potential degradants in reference to the known drug substance related impurities and degradants.
6. Clarify if the original method used by Propharma to analyze hydrocodone and guaifenesin in the drug product was ever validated. Provide the original method validation report, or validate it per ICH Q2 (R1).
7. Provide a validation report for the method used to analyze methylparaben and propylparaben in the drug product. The validation should be conducted per ICH Q2 (R1).
8. Provide representative chromatograms for related substance analysis for hydrocodone and guaifenesin in the drug product with appropriate zoom level to show adequate peak separation and proper integration. Address the following comments. The hydrocodone related substance chromatograms provided along with the batch analysis results are too crowded to identify individual peaks (b) (4)
(b) (4) The guaifenesin related

substance chromatogram has a unknown and placebo peak crowded together (b) (4)
It is not clear if the peaks are adequately separated.

9. Provide example chromatograms for the analysis of (b) (4) (methylparaben and propylparaben) in the drug product.
10. The provided stability data only support (b) (4) months expiry per ICH Q1E. Provide at least 12 month real time stability data to support the proposed two year shelf life.
11. Provide test method(s) for detection and quantification of container closure leachables (b) (4) along with appropriate validation information.
12. Clarify if the drug product manufacturing process is the same or equivalent to that used to manufacture the drug product for the clinical studies. Otherwise clarify the differences.
13. The CAS registry number provided for hydrocodone bitartrate drug substance is for the anhydrous form. The CAS registry number for the hydrated form is 34195-34-1. Correct the CAS registry number.
14. USP (b) (4) requires that (b) (4) on the product label; update the label accordingly.
15. In the Description section of the package insert, list the components of the oral solution in alphabetical order.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Swati Patwardhan, Regulatory Project Manager, at 301-796-4085.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

PRASAD PERI
04/28/2011



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

FACSIMILE TRANSMITTAL SHEET

DATE: April 5, 2011

To: Ms. Cassie Vitolo	From: Sadaf Nabavian
Company: Tiber Laboratories, LLC	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 1-678-208-0346	Fax number: 301-796-9728
Phone number: 1-678-208-0388	Phone number: 301-796-2777

Subject: NDA 22-424; Information Request

Total no. of pages including cover: 3

Comments: please confirm receipt. Thanks.

Document to be mailed: YES xNO

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Your submission dated November 29, 2010, to NDA 22-424, is currently under review and we have the following request for information:

1. For (b) (4) black raspberry flavor (b) (4) safety information on the flavoring agent as a whole or individual ingredients is not readily available. Provide information pertaining to the approved use of the flavoring in drugs or food in the U.S. and/or safety information for the flavoring agent as a whole or all individual ingredients.

Submit your response to Sadaf Nabavian, Regulatory Project Manager, via telephone facsimile to 301-796-9728 or email at Sadaf.Nabavian@fda.hhs.gov by COB on Monday, April 18, 2011. Your responses will subsequently need to be submitted officially to the NDA. If you have any questions, please contact Sadaf Nabavian, Regulatory Project Manager, at 301-796-2777.

NDA 22-424

SNabaivan/04.05.2011

SBarnes/04.05.2011

Glee/04.05.2011

TRobison/04.05.2011

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/s/

SADAF NABAVIAN
04/05/2011



NDA 22-424

FILING COMMUNICATION

Tiber Laboratories, LLC
5400 Laurel Springs Parkway
Suite 803
Suwanee, GA 30024

Attention: Cassie Vitolo
Director, Regulatory Affairs

Dear Ms. Vitolo:

Please refer to your New Drug Application (NDA) dated November 24, 2010, received November 29, 2010, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for hydrocodone bitartrate and guaifenesin oral solution.

We also refer to your submission dated January 06, 2011.

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 September 29, 2011.

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, mid-cycle, 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 post-marketing commitment requests by September 08, 2011.

In addition, during our filing review of your application, we identified the following potential review issue:

1. The two clinical pharmacology studies [BE (S09-0009) and food effect (S09-0010)] submitted for this NDA were previously submitted for NDA 22-279 for hydrocodone, pseudoephedrine and guaifenesin triple combination product (given

CR on Jan 25, 2011). For NDA 22-279, an audit performed by the Agency of studies S09-0009 (a drug-drug interaction and relative bioavailability study) and S09-0010 (a food effect study) identified deficiencies relating to (1) documentation irregularities, and (2) integrity of the bioanalytical data generated at the analytical site. Because of these deficiencies, these studies were not relied upon to support the clinical pharmacology of hydrocodone, pseudoephedrine, and guaifenesin oral solution. Therefore, these studies may not be used to support this NDA submission unless the deficiencies above have been addressed.

We are providing the above comment to give you preliminary notice of a potential review issue. 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 do not expect a response to this letter, and we may not review any such response during the current review cycle.

We also request that you submit the following information:

1. Provide published scientific literature and reports on carcinogenicity, mutagenicity, teratogenicity, effects on fertility, and acute and repeat dose adult animal studies for hydrocodone and guaifenesin.
2. Provide methods validation data for relevant non-compendial methods (e.g., chromatographic methods, microbiological assays) as per the ICH Q2A and Q2B guidances.
3. Provide for each batch of (b) (4) colors (Blue #1, Red #33) used to make the NDA batches an FDA certificate of batch certification.
4. Since the drug formulation contains significant levels of excipients (b) (4), provide data and controls for container closure component extractables (b) (4), and for leachables (b) (4). Alternatively, provide a data based justification for a lack of controls for extractables and leachables. For any extractables and leachables which were identified, provide a safety assessment of such extractables and leachables.
5. Provide 100% size color mockups of each actual carton and immediate container label.
6. Clarify that the formulation of drug product used for the clinical/bio studies was the same as that proposed for marketing.

7. Clarify the specifications for the drug product in section 3.2.P.5.1, which contains an assay for pseudoephedrine hydrochloride and its impurities. This appears to be an error.
8. Provide written methods for the microbial limits test procedure (b) (4) for the drug product, along with appropriate validation data.
9. We note that the proposed shelf life is 24 months even though you have provided (b) (4) months of real time data. As per the ICH Q1A guidance, a maximum (b) (4) shelf life may be granted provided the stability data are robust.

We also have the following labeling comments regarding conformance of your proposed labeling with the Physician Labeling Rule (PLR) format requirements. Submit revised labeling incorporating the following comments:

General Comments

1. For specific requirements on the content and format of labeling for human prescription drug and biologic products refer to 21 CFR 201.57. Also see Draft Guidance for Industry: Labeling for human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements (Implementation Guidance).
2. Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling format.

Highlights Section

3. Highlights, excluding the boxed warning, must be limited in length to one-half page (e.g., would fit on one-half page if printed on 8.5" x 11 paper, single spaced, minimum 8 point type with ½ inch margins on all sides, in a two-column format).
4. All headings and subheadings must be in bold type.
5. All headings must be presented in the center of a horizontal line in upper-case letters and bold type. The horizontal line can be a solid or dashed line.
6. For multiple subheadings, each subheading must be preceded by a bullet point.
7. There should be white space between each major heading in Highlights.
8. Required statement: Patient Counseling Information Statement (must appear in bold type).

9. Revise Date must appear in bold type.

Table of Contents

10. The heading – FULL PRESCRIBING INFORMATION: CONTENTS - must appear at the beginning of the table of contents in upper-case letters and bold type.
11. Use of a two-column format for the Table of Contents, and if possible, that it be limited in length to one-half page.
12. If the Highlights and Table of Contents do not fit on one page, insert the Table of Contents on page 2 of the labeling.
13. A horizontal line must be located between Highlights and Table of Contents to separate Highlights information from the table of contents. A horizontal line must also be located between the Table of Contents and the FPI.
14. Table of Contents subsection headings must be indented and not bolded and should be in lower-case letters.
15. When a section or subsection is omitted from the FPI such as in Section 7.3, the section or subsection must also be omitted from the Contents. The heading “Full Prescribing Information: Contents” must be followed by an asterisk and the following statement must appear at the end of the Contents: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
16. Create subsection headings that identify the content. Avoid using the words “General” “Other” “Miscellaneous” for a subsection heading (b) (4)
17. Avoid using acronyms in subsection headings. Spell out. For example, do not use “CNS Depressants” as a subsection heading.

Full Prescribing Information

18. The heading – FULL PRESCRIBING INFORMATION – must appear at the beginning of the FPI in upper-case letters and bold type.
19. The proprietary and established names can be repeated at the beginning of the FPI, or at the beginning of each page of the FPI (e.g., as a header), if this enhances product identification on subsequent pages of labeling (See Implementation Guidance - FAQ #4).
20. Bullet the indications in the FPI.

21. For each contraindication, use numbered subsection headings or bullets.

In addition to the labeling, also submit the electronic content of the labeling.

We request that you resubmit labeling that addresses these issues by February 21, 2011. 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.

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 sub-populations.

If you have any questions, call Sadaf Nabavian, Regulatory Project Manager, at (301) 796-2777.

Sincerely,

{See appended electronic signature page}

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

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/s/

LYDIA I GILBERT MCCLAIN
02/11/2011



FACSIMILE TRANSMITTAL SHEET

DATE: December 27, 2010

To:
Cassie Vitolo
Director, Regulatory Affairs

From: Swati Patwardhan
Regulatory Health Project Manager
Office of Pharmaceutical Science
Office of New Drug Quality Assessment
Division of Post-Marketing Evaluation

Company: Tiber Laboratories, LLC

Fax number: 678-208-0346

Fax number: 301-796-9748

Phone number: 678-208-0388

Phone number: 301-796-4085

Subject: Information Request for NDA 22-424

Total # of pages including cover: 2

Comments:

**Please acknowledge the receipt by email @
swati.patwardhan@fda.hhs.gov**

Original document to be mailed:

Yes

No

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We are reviewing CMC section of your NDA 22-424 and have following information request:

1. Clarify whether the drug substance manufacturers ^{(b) (4)}
 also perform release and stability testing of the drug substances.
2. For sites which have multiple addresses, clarify which sites are the manufacturing/testing facilities and which sites are other sites (e.g. headquarters).
3. Provide CFN numbers for the drug substance sites and certify that they are also ready for inspection.
4. Clarify that the list of sites in the attachment to Form 356h are complete.
5. Provide contact information for each drug substance site (i.e., contact person, telephone number, fax number, e-mail address).
6. Provide a statement pertaining to the cGMP status of each facility.

Provide a tentative timeline for the response.

Thank you
Swati Patwardhan

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/s/

SWATI A PATWARDHAN
12/27/2010



NDA 22424

NDA ACKNOWLEDGMENT

Tiber Laboratories, LLC
5400 Laurel Springs Parkway
Suite 803
Suwanee, GA 30024

Attention: Cassie Vitolo
Director, Regulatory Affairs

Dear Ms. Vitolo:

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

Name of Drug Product: Hydrocodone bitartrate and Guaifenesin Oral Solution
(2.5mg hydrocodone/5ml and 200 mg guaifenesin/5 ml)

Date of Application: November 24, 2010

Date of Receipt: November 29, 2010

Our Reference Number: NDA 22424

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 28, 2011, 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.

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>.

If you have any questions, call Sadaf Nabavian, Regulatory Project Manager, at (301) 796-2777.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Supervisory CPMS
Division of Pulmonary, Allergy, and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

SADAF NABAVIAN
12/13/2010



**Food and Drug Administration
Center for Drug Evaluation and
Research**

1 Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: April 11, 2007

To: Ray Farinas	From: Ladan Jafari
Company: propharma	Division of Pulmonary and Allergy Products
Fax number: 305-594-0988	Fax number: 301-796-9728
Phone number: 305-594-7645	Phone number: 301-796-1231

Subject: Pre-IND 76,365

Total Number of Pages Including Cover: 10

Comments: Pre-IND meeting minutes

Document to be mailed: YES NO

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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type: B
Meeting Category: Pre-IND
Meeting Date and Time: March 26, 2007 at 11:00 AM
Meeting Location: Conference room 1313
Application Number: Pre-IND 76,365
Product Name: guaifenesin/hydrocodone and
guaifenesin/hydrocodone and pseudoephedrin
Received Briefing Package February 7, 2007
Sponsor Name: Propharma
Meeting Requestor: Ray Farinas
Meeting Chair: Badrul Chowdhury, M.D., Ph.D.
Meeting Recorder: Ladan Jafari

Meeting Attendees:

Mr. Rey Farinas, Executive Vice President, Propharma

Soloman Goll, Quality Unit Manager, Propharma

(b) (4) Regulatory Consultant, (b) (4)
(b) (4) Toxicologist, (b) (4)

FDA Attendees:

Joe Sun, Ph.D., Supervisory Pharmacologist/Toxicologist

Emmanuel Fadiran, Clinical Pharmacology Team Leader

Xu Wang, M.D., Medical Reviewer

Charles Lee, M.D., Medical Team Leader

Prasad Peri, Ph.D., CMC, Pharmaceutical Assessment Lead

Badrul Chowdhury, M.D., Ph.D., Division Director

Sadaf Nabavian, Pharm.D., Regulatory Health Project Manager

Ladan Jafari, Regulatory Health Project Manager

Janice Weiner, J.D., M.P.H., Regulatory Counsel

BACKGROUND

Propharma submitted a meeting request dated December 14, 2006, to discuss submission of two separate applications for the combination of guaifenesin and hydrocodone oral solution and guaifenesin/hydrocodone and pseudoephedrine oral solution. Upon receipt of the meeting package dated February 6, 2007, the Division provided the following responses to Propharma's question via FAX. The content of that FAX is printed below. Any discussion that took place at the meeting is captured directly under the relevant original response including any changes in our original position. Propharma's questions are in ***bold italics***; FDA's response is in *Italics*; discussion is in normal font.

- 1. Does the Agency agree that the 505(b)(2) submission route is appropriate with the cited Listed Drugs being NDA 19-111 for Tussionex Suspension; NDA 5-213 for Hycodan Tablets and Syrup; and NDA 19-410 for Hycomine Syrup? Therefore, we request confirmation that the proposed 505(b)(2) NDA will qualify as a no user fee NDA.***

Response:

A 505(b)(2) NDA submission would be an acceptable approach based on the information provided. We recommend 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(s), 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(s). In this case, you should establish a "clinical bridge" between your proposed drug product and the listed drug(s) (e.g., via comparative bioavailability data) to demonstrate that reliance is appropriate. (In this regard, we note that Hycomine Syrup is no longer marketed.) 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.

The Division does not assess or waive user fees. User fees are based on the type of application and whether there is clinical data included in the submission. 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:

- Propharma inquired as to what type of bioavailability data are required for their immediate release formulations. Propharma indicated that they plan to provide bioavailability data for their immediate release formulations and not to include comparator arms for the reference products. Propharma asked if that approach is acceptable.
 - The Division agreed with the proposal and clarified that we are requesting this information to know if the systemic exposure from their product is comparable to those approved previously. Such a cross-study comparison is acceptable to the Division for these proposed oral solution formulations.
- Propharma asked if it is acceptable to do a small bioavailability study to compare their products versus those approved previously. Propharma asked if they need to do the bioavailability study under an IND.
 - The Division agreed that a small bioavailability study is sufficient. The Division agreed that any such study should be performed under an IND. Propharma is encouraged to submit a protocol to the Division for review.

2. ***Does the Agency concur that the available regulatory information cited fully supports the safety and efficacy of the active ingredients guaifenesin and pseudoephedrine hydrochloride, i.e., the OTC monograph for expectorant drug products and nasal decongestant drug products? Guaifenesin is an accepted expectorant (Part 341.20) in the OTC drug monograph, Part 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. The cited information fulfills all filing requirements (except CMC) for the NDAs.***

4. ***Does the Agency concur that 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 base (Rx only). The opioid, hydrocodone Bitartrate, has been the subject of numerous NDAs approved by the Agency for its therapeutic use as an antitussive.

Response to questions 2 and 4:

We do not concur. The safety and efficacy of the active ingredients guaifenesin and pseudoephedrine hydrochloride may be supported by the OTC monograph for expectorant drug products and nasal decongestant drug products when used at doses, for indications, in combinations, and with labeling specified by the OTC monograph.

[REDACTED] (b) (4)

The safety and efficacy of hydrocodone bitartrate may be supported by the Agency's findings of efficacy and safety for approved NDA antitussive products containing hydrocodone bitartrate.

[REDACTED] (b) (4)

Discussion:

- Propharma asked for clarification regarding the dosing regimen [REDACTED] (b) (4)
[REDACTED]
 - The Division stated that Propharma must adhere to the dose recommendation [REDACTED] (b) (4) as specified in the OTC monograph and by the label for the reference hydrocodone product

Clinical trials will be necessary to support the safety and efficacy of your products [REDACTED] (b) (4). Alternatively, you may choose to revise your dosing recommendations or reformulate your products to meet the dosages specified in OTC monograph and the reference hydrocodone product.

The cited information does not fulfill all filing requirements for the planned NDA submission. You must provide data to demonstrate that there are no drug-drug interactions for the ingredients in your products. These data may come from the medical literature, if available, or from conducting clinical pharmacology studies. In addition, you will need to provide additional safety information (see Question 3).

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

Response:

Yes, a safety update report for the listed drugs will be required. A survey of the available clinical and non-clinical literature, United States and international post-marketing adverse event databases, international regulatory actions to support the safety and efficacy of the proposed drug products is required. Address overdose, drug abuse, and use of the ingredients in special populations, such as pregnant and lactating women, the elderly, children, by race, by gender, and in patients with hepatic and renal impairment in your NDA application.

- 5. Propharma believes that the reference to approved NDA products and the OTC monograph evaluation are sufficient to meet the preclinical requirements for guaifenesin, pseudoephedrine hydrochloride and hydrocodone bitartrate. Does the Agency concur?**

Response:

We concur that reliance on the Agency's finding of safety and/or effectiveness for the listed drugs referenced in question 1 and the OTC monograph evaluation is adequate to meet the preclinical requirements for the three drug substances. Submit such preclinical information and references in the pertinent sections of the NDA (see also response to question 1).

6. *Propharma believes that because the two drug products are immediate release oral solution products there is no pharmacokinetic requirement to demonstrate the immediate availability of the drugs in vivo. Does the Agency concur?*

Response:

We concur. However, we recommend that you provide information on whether the combination of guaifenesin and pseudoephedrine HCl has an effect on the pharmacokinetics of hydrocodone and vice versa. This information may be provided from the literature or by conducting a pharmacokinetic drug-drug interaction study. We also recommend that you provide information from literature on the food effects on the formulation based on information on the individual drug components.

Discussion:

- Propharma indicated that both guaifenesin and pseudoephedrine are readily absorbed and that data on drug-drug interaction is already available on Mucinex-D. Propharma asked if the Division needed any other drug-drug interaction study.
 - The Division recommended that Propharma provide any supporting data for drug-drug interaction for the three-ingredient combination product available in the literature. In addition, the Division reminded Propharma that any food effect should be addressed in the labeling of their products and this information may also be obtained from published literature as noted in the FDA response.

7. *Propharma plans to seek a waiver from conducting pediatric studies under the Pediatric Research Equity Act. This drug product is not likely to be used in a substantial number of pediatric patients,* (b) (4)

Does the Agency concur?

Response:

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 applications. 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/cder/pediatric/>) and in the Draft Guidance for Industry: How to Comply with the Pediatric Research Equity Act (September 7, 2005), available at <http://www.fda.gov/cder/guidance/6215dft.pdf>.

We also have the following additional comments:

- 1. Your proposed indications are not acceptable. The indications should be guided by the OTC monograph labeling for expectorant drug products (21 CFR 341.78), the OTC monograph labeling for nasal decongestant drug products (21 CFR 341.80), and the DESI notice for hydrocodone bitartrate (Hycodan, 47 FR 23809, June 1, 1982).*

Discussion:

- Propharma indicated that they plan to seek indication [REDACTED] (b) (4) [REDACTED] Propharma asked if this approach was acceptable.
 - The Division suggested that Propharma also look at other approved prescription products such as Codeprex (NDA 21-369) as a guide to see how the indication section of the labeling of those products are written.
- 2. In your submission, you refer to a number of unapproved hydrocodone antitussive products [REDACTED] (b) (4) [REDACTED] [page 22]. Note that you will not be able to support the efficacy and safety of your products with references to unapproved products.*

Specific reference may also be made to the multi-disciplinary "Guidance for Industry: Content and Format of Investigational New Drug Applications (INDs) for Phase I Studies of Drugs, Including Well-Characterized, Therapeutic Biotechnology derived Products," as well as the CMC guidance, "Guidance for Industry: INDs for Phase 2 and Phase 3 Studies." We also refer you to :

http://www.fda.gov/cder/drug/unapproved_drugs/presentations/nasr.pdf

3. *In addition, special considerations should be given for impurities in hydrocodone that constitute a structural alert. Refer to ICHQ3A(R) for approaches to qualifying them.*

Discussion:

- Propharma indicated that a potential impurity has been identified ^(b)₍₄₎ and has been shown to be negative for genotoxicity and is handled as an ordinary impurity subject to ICHQ3A limits. Propharma also indicated that the NDA will contain reference to the ^(b)₍₄₎ Drug Master File (Propharma's raw material source), which contains qualification information for the impurity. Propharma asked if this was adequate or are there any other impurities that the Division is concerned about.
- The Division responded that it is acceptable to provide a DMF or an authorization letter to an appropriate DMF for their product. The Division further reminded Propharma that it is the responsibility of the applicant to identify and qualify any impurities that are considered as structural alerts.

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/s/

Ladan Jafari
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