

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207916Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 207916

SUPPL #

HFD # 180

Trade Name Cetylev

Generic Name (acetylcysteine) effervescent tablets

Applicant Name Arbor Pharmaceuticals, LLC

Approval Date, If Known January 29, 2016

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) NDA

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.

A open-label bioequivalence study only was performed by the applicant to bridge to the relied upon listed drug (Mucomyst). The applicant also submitted published literature to support some labeling changes. The studies in the published literature are not adequate or well controlled, are not "new," and were not "conducted or sponsored by" the applicant.

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?

7 years Orphan Drug Exclusivity

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# 13601 Mucomyst (acetylcysteine) Oral Solution for Inhalation

NDA# 21539 Acetadote (acetylcysteine) Injection

NDA# 17366 Mucomyst with Isoproterenol (acetylcysteine and isoproterenol hydrochloride) Solution for Inhalation

2. Combination product.

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

YES NO

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

YES NO

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

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

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

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

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

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

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

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

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

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

not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

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

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

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

YES NO

If yes, explain:

Name of person completing form: Lara Dimick-Santos, M.D.
Title: Medical Officer
Date: 11/5/15

Name of Office/Division Director signing form: Joyce Korvick, M.D.
Title: Deputy Director of Safety, DGIEP

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/

ANISSA A DAVIS
01/28/2016

JOYCE A KORVICK
01/29/2016



1.3. Administrative Information

3. DEBARMENT CERTIFICATION

Arbor Pharmaceuticals, LLC hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

A handwritten signature in cursive script, appearing to read "Mary Lou Freathy", written over a horizontal line.

Mary Lou Freathy
VP, Regulatory Affairs, Quality, & Manufacturing
Arbor Pharmaceuticals, LLC

A handwritten date "June 19, 2015" written in cursive script over a horizontal line.

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 207916 BLA # n/a	NDA Supplement # n/a BLA Supplement # n/a	If NDA, Efficacy Supplement Type: n/a <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: CETYLEV Established/Proper Name: acetylcysteine Dosage Form: effervescent tablets for oral solution		Applicant: Arbor Pharmaceuticals, LLC Agent for Applicant (if applicable): n/a
RPM: CDR Anissa Davis-Williams		Division: Division of Gastroenterology and Inborn Errors 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 (notify CDER OND IO) Date of check: 12/07/15</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 <u>January 30, 2016</u> 		<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"/> None
❖ 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 Characteristics³		

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.

Review priority: Standard Priority
 Chemical classification (new NDAs only): Type 3
 (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 checked="" type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
 Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

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 (approvals only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other (Tweet via social media)
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ 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 (approvals only)	<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 (including approval letter with final labeling)	Action(s) and date(s): 1/29/16
Labeling	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
• Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	<input checked="" type="checkbox"/> Included
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
• Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	<input checked="" type="checkbox"/> Included
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
• Most-recent draft labeling	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
• Acceptability/non-acceptability letter(s) (indicate date(s))	6/25/15
• Review(s) (indicate date(s))	6/22/15
❖ Labeling reviews (indicate dates of reviews)	RPM: <input type="checkbox"/> None 4/27/15 DMEPA: <input type="checkbox"/> None 1/28/16;1/13/16; 12/18/15 DMPP/PLT (DRISK): <input type="checkbox"/> None 12/7/15 OPDP: <input type="checkbox"/> None 12/2/15 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input type="checkbox"/> 11/9/15-pgs. 137-144 Other: <input type="checkbox"/> None DMPH (Pediatrics)-10/29/15 DMPH (Maternal Health)- 11/12/15
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (indicate date of each review)	5/29/15
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2) 12/22/15
❖ NDAs only: Exclusivity Summary (signed by Division Director)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	

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

<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 type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ 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: <u>indication granted orphan designation on 2/24/15</u> 	
<ul style="list-style-type: none"> ❖ Breakthrough Therapy Designation 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	
<ul style="list-style-type: none"> CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	
<ul style="list-style-type: none"> ❖ 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, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include previous action letters, as these are located elsewhere in package</i>) 	1/28/16;1/27/16;1/21/16;1/19/16;1/11/16;12/16/15;10/22/15;10/21/15;9/25/15;9/10/15;9/9/15;8/25/15;8/6/15;7/31/15;6/30/15;6/20/15;5/29/15;5/6/15;4/8/15
<ul style="list-style-type: none"> ❖ 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) 	
<ul style="list-style-type: none"> ❖ 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 checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<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 checked="" type="checkbox"/> N/A
<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 focused milestone meetings) (<i>indicate dates of mtgs</i>) 	2/27/13 (Pre-IND meeting)
<ul style="list-style-type: none"> ❖ 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	
<ul style="list-style-type: none"> ❖ 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 1/29/16
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 1/5/16
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None

Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review 11/20/15;5/14/15(concur)
• Clinical review(s) (<i>indicate date for each review</i>)	11/20/15;5/14/15
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input 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>)	1/22/16
❖ 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"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review 1/5/16
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 1/5/16
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input type="checkbox"/> None requested 8/31/15; 7/1/15

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review 1/28/16;11/19/15;5/13/15(concur)
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 1/28/16;11/19/15;5/13/15
❖ 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 Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• Tertiary review (<i>indicate date for each review</i>)	<input type="checkbox"/> None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 1/28/16 (CMC);11/11/15 (Microbiology concur); 11/10/15 (Biopharmaceuticals concur); 11/9/15 (CMC concur);
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 1/28/16 (CMC);11/11/15 (Microbiology); 11/10/15 (Biopharmaceuticals); 11/9/15 (CMC); 5/29/15 (filing review-CMC and Biopharmaceuticals)
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<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</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	11/10/15 (Page 132 of Integrated Quality Assessment combined review)
<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"/> Facilities inspections (<i>action must be taken prior to the re-evaluation date</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

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>)
❖ For products that need to be added to the flush list (generally opioids): Flush List <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input checked="" type="checkbox"/> Done
❖ 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 checked="" 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 type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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/s/

ANISSA A DAVIS
01/29/2016

BRIAN K STRONGIN
02/03/2016

Davis, Anissa

From: Davis, Anissa
Sent: Thursday, January 28, 2016 2:56 PM
To: 'Allison Lowry'
Cc: Korvick, Joyce A
Subject: RE: NDA 207916 Cetylev Labeling Negotiations
Attachments: Cetylev Labeling (PI) Changes 1.28.16.docx

Importance: High

Hello Allison:

Attached are our edits to the label for NDA 207916 Cetylev. Utilize this version to make your edits and submit your version officially to your application today if you do not have any other questions or concerns. Thanks

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.
CDR, United States Public Health Service (USPHS)
Senior Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
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From: Allison Lowry [<mailto:alowry@arborpharma.com>]
Sent: Thursday, January 28, 2016 11:54 AM
To: Davis, Anissa
Subject: RE: NDA 207916 Cetylev Labeling Negotiations

Hi Anissa,

Since the recommended dosing (section 2.3) is based on body weight, we are wondering if the added paragraph in section 8.6 may be misinterpreted. (b) (4)

so we believe the more accurate way to address the risk is to refer clinicians to the table that addresses sodium content in each tablet so that they can calculate an accurate dose.

We are proposing to replace the second paragraph in section 8.6 with the following:

“If sodium intake is a concern (b) (4), please refer to Table 3 for (b) (4) sodium (b) (4) and to Tables 1 and 2 for recommended dosage (b) (4) based on body weight.”

The PPI should be ok.

Should we add this proposal in our revised submission or would you like to confirm it's ok with your reviewer before we submit?

Many thanks –
Allison

Allison Lowry
Director, Regulatory Affairs
Arbor Pharmaceuticals, LLC
Direct: 678-334-2428

From: Davis, Anissa
Sent: Wednesday, January 27, 2016 4:16 PM
To: Allison Lowry (ALowry@arborpharma.com)
Cc: Korvick, Joyce A
Subject: NDA 207916 Cetylev Labeling Negotiations
Importance: High

Hello Allison:

We have reviewed the edited labeling information for NDA 207916 Cetylev (acetylcysteine) effervescent tablets and made additional edits. Please review the attached revisions of the Prescribing Information (PI) and the Patient Package Insert (PPI). **Ensure all edits made by you are kept in track change format and do not accept the edits (if any). If you are in agreement with the FDA revisions, accept the track changes (additions and/or deletions).**

Prescribing Information:

<< File: Cetylev Labeling (PI) Changes 1.27.16.docx >> << File: Cetylev Labeling (PI) Changes 1.27.16.pdf >>

Patient Package Insert:

<< File: cetylev-patient-pi-changes 1.27.16.docx >> << File: cetylev-patient-pi-changes 1.27.16.pdf >>

Please submit your response officially to your application by Thursday, January 28, 2016.

Thank You!

Anissa

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Food and Drug Administration

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ANISSA A DAVIS
01/28/2016

Davis, Anissa

From: Davis, Anissa
Sent: Wednesday, January 27, 2016 4:16 PM
To: Allison Lowry (ALowry@arborpharma.com)
Cc: Korvick, Joyce A
Subject: NDA 207916 Cetylev Labeling Negotiations

Importance: High

Hello Allison:

We have reviewed the edited labeling information for NDA 207916 Cetylev (acetylcysteine) effervescent tablets and made additional edits. Please review the attached revisions of the Prescribing Information (PI) and the Patient Package Insert (PPI). **Ensure all edits made by you are kept in track change format and do not accept the edits (if any). If you are in agreement with the FDA revisions, accept the track changes (additions and/or deletions).**

Prescribing Information:



Cetylev Labeling (Cetylev Labeling)
190 C:\hannegsa... 190 C:\hannegsa...

Patient Package Insert:



ew-patient-pi-dhalew-patient-pi-dha
1,2... 1,2...

Please submit your response officially to your application by Thursday, January 28, 2016.

Thank You!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

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ANISSA A DAVIS
01/27/2016

Davis, Anissa

From: Davis, Anissa
Sent: Thursday, January 21, 2016 11:30 AM
To: Allison Lowry (ALowry@arborpharma.com)
Subject: NDA 207916: Labeling (Blister labels) Change Requested

Importance: High

Hello Allison:

Regarding NDA 207916 Cetylev (acetylcysteine) effervescent tablets, please make the following changes to your labeling:

- **Please revise the drug product name on the blisters as shown below to be consistent with the carton labeling and submit it.**
Cetylev
(acetylcysteine) effervescent tablets for oral solution

Please submit your response officially to your application by Monday, January 25, 2016 or sooner.

Thanks!

Anissa

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ANISSA A DAVIS
01/21/2016

Davis, Anissa

From: Davis, Anissa
Sent: Tuesday, January 19, 2016 5:56 PM
To: Allison Lowry (ALowry@arborpharma.com)
Subject: NDA 207916: Labeling Negotiations

Importance: High

Hello Allison:

We have reviewed the Prescribing Information (PI) for NDA 207916 Cetylev (acetylcysteine) effervescent tablets and made additional comments/edits (formatting was corrected as well). Please review. **As before, please ensure all edits made by you are kept in track change format and do not accept the edits. If you are in agreement with the FDA revisions, accept the track changes (additions and/or deletions).**



Cetylev PI to Applicant L.L.L.L... Cetylev PI to Applicant L.L.L.L...

Please submit your response officially to your application by Friday, January 22, 2016 or sooner.

Thanks!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

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ANISSA A DAVIS
01/19/2016

Davis, Anissa

From: Davis, Anissa
Sent: Monday, January 11, 2016 12:31 PM
To: Allison Lowry (ALowry@arborpharma.com)
Subject: NDA 207916 Cetylev (acetylcysteine) effervescent tablets: Labeling Negotiations

Importance: High

Hello Allison:

We have reviewed the edited/revised labeling information for NDA 207916 Cetylev (acetylcysteine) effervescent tablets and made additional comments/edits. Comments regarding the Carton and Container are below as well. Please review the attached revisions in pdf and word versions of the PI.

Prescribing Information:



Cetylev PI (edited) Cetylev PI (edited)
1.1.1.16 - io A... 1.1.1.16 - io A...

Carton labeling:

1. We recommend increasing the prominence of the established name and dosage form using bold in accordance with 21 CFR 201.10(g)(2), taking into account all pertinent factors, including typography, layout, contrast, and other printing features.
2. We recommend increasing the prominence of the strength by increasing the print size (and colored box) to further emphasize this pertinent information. As currently presented, the statement "LEMON MINT FLAVOR" competes in size and prominence with the product strength, which is considered essential information on the carton labeling.
3. We recommend revising the dosage form to include the complete dosage form with route of administration for consistency with USP General Chapter <1121> Nomenclature requirements. We recommend the following:

Cetylev
(acetylcysteine) effervescent tablets for oral solution
500 mg

Patient Package Insert:

The division has agreed to your edits in the PPI. The copy below will be deemed final, if you agree. Please let me know.



Cetylev PPI final.docx Cetylev PPI final.pdf
1.1.1.16 - io A... 1.1.1.16 - io A...

Ensure all edits made by you are kept in track change format and do not accept the edits. If you are in agreement with the FDA revisions, accept the track changes (additions and/or deletions).

Please submit your response officially to your application by Friday, January 15, 2016.

Thanks



Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

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ANISSA A DAVIS
01/11/2016

Davis, Anissa

From: Davis, Anissa
Sent: Wednesday, December 16, 2015 4:22 PM
To: Allison Lowry (ALowry@arborpharma.com)
Subject: NDA 207916 Cetylev (acetylcysteine) effervescent tablets: Labeling Negotiations and PMR/PMC Information Email

Importance: High

Hello Allison:

We have reviewed your labeling information for NDA 207916 Cetylev (acetylcysteine) effervescent tablets and made significant changes. Due to the formatting issues that can arise for the Patient Package Insert (PPI), we have placed this document separately from the Prescribing Information (PI). Comments regarding the Carton and Container are below as well. Please review the attached revisions in pdf and word versions of the PI and PPI. **Ensure all edits made by you are kept in track change format and do not accept the edits. If you are in agreement with the FDA revisions, accept the track changes (additions and/or deletions). This is to be done for both, PI and PPI.**

Additionally, we do not have plans for you to conduct any postmarketing requirements/commitments at this time.

- **Prescribing Information**



- **Patient Package Insert**



- **Carton and Container**

- A. **Carton Labels**

1. We recommend revising the established name and dosage form font color to the same color as the proprietary name in accordance with 21 CFR 201.10(g)(2), to increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features.
2. We recommend modifying the font color of the statement "LEMON MINT FLAVOR" to a font color that would decrease the prominence of this statement as it distracts from the proprietary name, established name, dosage form, and strength. Additionally, we recommend removing the bolding from this statement as well.

- B. **Blister Pack Labels**

1. See comment A.2
2. Please submit blister pack labels including the lot number & expiration date.
3. We recommend having the product strength expressed in mg per single unit to make it clear the designated strength is per unit.

Please submit your response (clean and track change pdf and word version) officially to your application and a “true and exact” copy to me via email by January 4, 2016.

Thank you!

Anissa

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ANISSA A DAVIS
12/16/2015

Davis, Anissa

From: Davis, Anissa
Sent: Thursday, October 22, 2015 4:02 PM
To: Allison Lowry (ALowry@arborpharma.com)
Subject: NDA 207916 (acetylcysteine) effervescent tablets: Clinical/Labeling Information Request

Hello Allison:

We refer to your New Drug Application (NDA) 207916 Cetylev (acetylcysteine) effervescent tablets, submitted on March 30, 2015 pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA).

We have the following clinical/labeling information request:

Please provide literature support to justify that at times continued administration of CETYLEV may be necessary if there are still detectable levels of acetaminophen at the end of the maintenance dosing to support the following addition in the labeling.

Continued Therapy After Completion of Loading and Maintenance Doses

In cases of suspected massive overdose, or with concomitant ingestion of other substances, or in patients with preexisting liver disease, the absorption and/or the half-life of acetaminophen may be prolonged, in such cases consideration should be given to the need for continued treatment with CETYLEV. Acetaminophen levels and ALT/AST & INR should be checked after the last maintenance dose. If acetaminophen levels are still detectable, or (b) (4) the ALT/AST are still increasing or the INR remains elevated, the maintenance doses should be continued, and the treating physician should contact a US regional poison center at 1-800-222-1222, or alternatively, a “special health professional assistance line for acetaminophen overdose” at 1-800-525-6115 for assistance with dosing recommendations.

Please also provide literature to justify dosing for pts weighing (b) (4) kg to support the proposed following addition to the labeling.

(b) (4)

Please submit your response officially to your application by October 30, 2015.

Thank you!

Anissa

*Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.
CDR, United States Public Health Service (USPHS)
Senior Regulatory Project Manager*

Food and Drug Administration
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ANISSA A DAVIS
10/22/2015

Davis, Anissa

From: Davis, Anissa
Sent: Wednesday, October 21, 2015 12:12 PM
To: Allison Lowry (ALowry@arborpharma.com)
Subject: NDA 207916 (acetylcysteine) effervescent tablets: Clinical/Labeling Information Request

Hello Allison:

We refer to your New Drug Application (NDA) 207916 Cetylev (acetylcysteine) effervescent tablets, submitted on March 30, 2015 pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA).

-Please provide literature to support inclusion in the labeling of indications for treatment of both acute acetaminophen ingestion and repeated suprathreshold ingestion (RSI).

Please submit your response officially to your application by October 30, 2015.

Thank you!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

CDR, United States Public Health Service (USPHS)

Senior Regulatory Project Manager

Food and Drug Administration

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ANISSA A DAVIS
10/21/2015

Davis, Anissa

From: Davis, Anissa
Sent: Friday, September 25, 2015 4:01 PM
To: 'bwarren@arborpharma.com'
Cc: Allison Lowry (ALowry@arborpharma.com)
Subject: NDA 207916 (acetylcysteine): Labeling

Hello Briana:

Since Allison is out until Monday, please see the information below.

We are reviewing the label for NDA 207916 and have the following labeling information request:

- Section 12.3 (Pharmacokinetics) in the Prescribing Information currently contains information on [REDACTED] (b) (4). However, this information is not consistent with current labeling regulations and guidances. Therefore, please provide a revised Section 12.3 which follows the Clinical Pharmacology draft labeling guidance:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM109739.pdf>

Please use the pharmacokinetic information obtained from dosing healthy subjects with Cetylev tablets in the BE study (include study number) to write this section. In addition, you should also perform a literature search to obtain any additional information that would provide additional knowledge on the ADME of acetylcysteine in humans. Provide the complete publications to support any information added to the PI.

Please submit your response officially to your application by October 6, 2015!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.
CDR, United States Public Health Service (USPHS)
Senior Regulatory Project Manager
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/s/

ANISSA A DAVIS
09/25/2015

Davis, Anissa

From: Davis, Anissa
Sent: Thursday, September 10, 2015 1:16 PM
To: Allison Lowry (ALowry@arborpharma.com)
Subject: RE: NDA 207916: Labeling Information Request- Revised

Allison:

The highlighted sections below are changes to the IR. The reviewer noted the mistake today and wanted me to send it to you. Please revise as such. Thanks

- The drug product name on the immediate container labels should be displayed as shown below. XXX = 500 mg or 2.5 g

CETYLEV
(acetylcysteine) effervescent tablets
XXX

- Display “Rx Only”
- Submit revised 500 mg and 2.5 g immediate container labels.

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

CDR, United States Public Health Service (USPHS)

Senior Regulatory Project Manager

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From: Davis, Anissa
Sent: Wednesday, September 09, 2015 12:54 PM

To: Allison Lowry (ALowry@arborpharma.com)
Subject: NDA 207916: Labeling Information Request
Importance: High

Hello Allison:

We refer to your New Drug Application (NDA) 207916 Cetylev (acetylcysteine) effervescent tablets, submitted on March 30, 2015 pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA).

We are reviewing your application and have the following labeling (immediate container, 2-count blister pack) information request:

- The drug product name on the immediate container labels should be displayed as shown below. XXX = 500 mg or 2.5 gm

*CETYLEV
(acetylcysteine) effervescent tablets
XXX*

- Display “Rx Only”
- Submit revised 500 mg and 2.5 gm immediate container labels.

Please submit your response officially to your application by September 23, 2015.

Thank you!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

CDR, United States Public Health Service (USPHS)

Senior Regulatory Project Manager

Food and Drug Administration

Center for Drug Evaluation and Research

White Oak Building 22 Room: 5378

10903 New Hampshire Avenue

Silver Spring, Maryland

*Use zip code **20903** if shipping via United States Postal Service (USPS)*

(301) 796-5016 (office)

(301) 796-9904 (fax)

Anissa.Davis@fda.hhs.gov

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/s/

ANISSA A DAVIS
09/10/2015

Davis, Anissa

From: Davis, Anissa
Sent: Wednesday, September 09, 2015 12:54 PM
To: Allison Lowry (ALowry@arborpharma.com)
Subject: NDA 207916: Labeling Information Request

Importance: High

Hello Allison:

We refer to your New Drug Application (NDA) 207916 Cetylev (acetylcysteine) effervescent tablets, submitted on March 30, 2015 pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA).

We are reviewing your application and have the following labeling (immediate container, 2-count blister pack) information request:

- The drug product name on the immediate container labels should be displayed as shown below. XXX = 500 mg or 2.5 gm

*CETYLEV
(acetylcysteine) effervescent tablets
XXX*

- Display “Rx Only”
- Submit revised 500 mg and 2.5 gm immediate container labels.

Please submit your response officially to your application by September 23, 2015.

Thank you!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

CDR, United States Public Health Service (USPHS)

Senior Regulatory Project Manager

Food and Drug Administration

Center for Drug Evaluation and Research

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/s/

ANISSA A DAVIS
09/09/2015



NDA 207916

INFORMATION REQUEST

Arbor Pharmaceuticals, LLC
Attention: Allison Lowry
Director, Regulatory Affairs
6 Concourse Parkway
Suite 1800
Atlanta, GA 30328

Dear Ms. Lowry:

Please refer to your New Drug Application (NDA) dated March 30, 2015, received March 30, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Cetylev (acetylcysteine) effervescent tablets, 500 mg and 2 g.

On December 4, 2014, the Food and Drug Administration published the "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling," also known as the Pregnancy and Lactation Labeling Rule (PLLR) (79 FR 72064). According to PLLR, Risk Summary statements for sections 8.1 (Pregnancy), 8.2 (Lactation), and 8.3 (Females and Males of Reproductive Potential) must be based on available human and nonclinical data. The Risk Summary must also state when there are no human data or when available human data do not establish the presence or absence of drug-associated risk (21 CFR 201.57(c)(9)(i)(B)(1)).

The PLLR went into effect on June 30, 2015. As your NDA was submitted before that date, compliance with PLLR is voluntary. We note that you have attempted to follow the requested format and structure of PLLR, but during our review of your submitted labeling, we found that you have not provided information to support the labeling content for sections 8.1 and 8.2 of the labeling. More specifically, you have not reviewed and provided summaries of the available published human data.

As noted earlier, compliance with PLLR is voluntary for this application, but we highly encourage you to comply. To comply, you should review and summarize the literature and reports from your pharmacovigilance database with regard to oral acetylcysteine use in pregnancy and lactation. **Resubmit revised labeling and a summary of the available data by September 1, 2015.**

The revised labeling will be used for further labeling discussions. Refer to the Guidance for

Industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>). Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

If you have any questions, please contact CDR Anissa Davis-Williams, Senior Regulatory Project Manager, at (301) 796-5016.

Sincerely,

{See appended electronic signature page}

Anissa Davis-Williams, RN, B.S.N., M.P.H.,
C.P.H.M.
CDR/USPHS
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

ANISSA A DAVIS
08/25/2015



NDA 207916

INFORMATION REQUEST

Arbor Pharmaceuticals, LLC
Attention: Tina Morton
Senior Manager, Regulatory Affairs
6 Concourse Parkway, Suite 1800
Atlanta, GA 30328

Dear Ms. Morton:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Acetylcysteine Effervescent Tablets, 500 mg and 2.5 g

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a written response by August 14, 2015, in order to continue our evaluation of your NDA.

Drug Product

1. Please send 3 to-be marketed 2-tablet blister packs (0.5 g and 2.5 g) with tablets in them.

Biopharmaceutics

1. In M. 2.3.P.2 Pharmaceutical Development section, page 20, you mentioned the mean disintegration (effervescence) time on the lowest dose ($(b)(4)$ g NAC in 300 mL water) and the highest dose (15 g NAC in 300 mL water) is about $(b)(4)$ seconds (for the $(b)(4)$ g dose where $(b)(4)$ g NAC tablets are dissolved in water) to about $(b)(4)$ seconds (for the 15 g dose where six 2.5 g NAC tablets are dissolved in water).

Provide the detailed batch information (i.e. Batch No., Manufacturing date, Expiration date, Trial #, etc.), individual disintegration time, and average disintegration time of your drug product to be administered in multiple NAC combination from $(b)(4)$ to 15 g in 300 mL of purified water.

If you have any questions, please contact Heather Strandberg, Senior Regulatory Health Project Manager, at (240) 402-9096.

Sincerely,

Moojhong Rhee -S

Digitally signed by Moojhong Rhee -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Moojhong Rhee -S,
0.9.2342.19200300.100.1.1=1300041261
Date: 2015.08.06 17:16:32 -04'00'

Moo-Jhong Rhee, Ph.D.
Chief, Branch V
Division of New Drug Products II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Davis, Anissa

From: Davis, Anissa
Sent: Friday, July 31, 2015 10:25 AM
To: Allison Lowry (ALowry@arborpharma.com)
Subject: NDA 207916 Cetylev (acetylcysteine) effervescent tablets:CMC Information Request

Importance: High

Hello Allison:

Please refer to your New Drug Application (NDA), 207916 Cetylev (acetylcysteine) effervescent tablets, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA).

We are conducting a review of your application and have the following information request:

- We were unable to locate the records for the **stabilization procedures used/followed at the clinical site during blood sample collection and processing.**

Please provide these records as it is available from the clinical site study binder, as they are needed to assess and facilitate data review.

Please submit your response officially to your application and a courtesy email copy to me by August 5, 2015.

Thank you!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

CDR, United States Public Health Service (USPHS)

Senior Regulatory Project Manager

Food and Drug Administration

Center for Drug Evaluation and Research

White Oak Building 22 Room: 5378

10903 New Hampshire Avenue

Silver Spring, Maryland

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(301) 796-9904 (fax)

Anissa.Davis@fda.hhs.gov

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/s/

ANISSA A DAVIS
07/31/2015

Davis, Anissa

From: Davis, Anissa
Sent: Tuesday, June 30, 2015 12:09 PM
To: Allison Lowry (ALowry@arborpharma.com)
Subject: NDA 207916: Nonclinical Information Request

Hello Allison:

We refer to your New Drug Application (NDA) 207916 Cetylev (acetylcysteine) effervescent tablets, submitted on March 30, 2015 pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA). We are reviewing your application and have the following nonclinical information request:

Please submit the following publication officially to your NDA for review-

- Bonanomi L, Gazzaniga A. Toxicological, pharmacokinetic and metabolic studies on acetylcysteine. *Eur J Respir Dis*, 1981; 61 (Suppl III): 45-51.

Please submit by July 10, 2015.

Thank you!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

CDR, United States Public Health Service (USPHS)

Senior Regulatory Project Manager

Food and Drug Administration

Center for Drug Evaluation and Research

White Oak Building 22 Room: 5378

10903 New Hampshire Avenue

Silver Spring, Maryland

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(301) 796-9904 (fax)

Anissa.Davis@fda.hhs.gov

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/s/

ANISSA A DAVIS
06/30/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 207916

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Arbor Pharmaceuticals, LLC
6 Concourse Parkway, Suite 1800
Atlanta, GA 30328

ATTENTION: Allison Lowry
Director, Regulatory Affairs

Dear Ms. Lowry:

Please refer to your New Drug Application (NDA) dated and received March 30, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Acetylcysteine Effervescent Tablets, 500 mg and 2500 mg.

We also refer to your correspondence, dated and received April 1, 2015, requesting review of your proposed proprietary name, Cetylev.

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

If any of the proposed product characteristics as stated in your April 1, 2015, submission 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 Aleksander Winiarski, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5295. For any other information regarding this application, contact Anissa Davis, Regulatory Project Manager in the Office of New Drugs, at (301) 796-5016.

Sincerely,

{See appended electronic signature page}

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

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/s/

TODD D BRIDGES
06/25/2015



NDA 207916

INFORMATION REQUEST

Arbor Pharmaceuticals, LLC
Attention: Tina Morton
Senior Manager, Regulatory Affairs
6 Concourse Parkway, Suite 1800
Atlanta, GA 30328

Dear Madam:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Acetylcysteine Effervescent Tablets, 500 mg and 2.5 g.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a written response by July 17, 2015 in order to continue our evaluation of your NDA.

1. We note that Edetate Disodium is (b) (4)
(b) (4)
Edetate Disodium, which is added as (b) (4)% of the total composition, and discuss the (b) (4). We have noted that a specification for Edetate Disodium is not included in drug product release and stability, so please provide applicable details on (b) (4) and available test results for Edetate Disodium (b) (4).
2. With regard to proposed in-process controls provided on Table 1 and Table 2 of 3.2.P.3.4, provide details on test methods and validation reports, as applicable. If you have already provided the information in the submission, please point us to the location with section and page number.
3. For an effervescent tablet for oral solution, (b) (4)
(b) (4) may be critical to control the physical characteristics of the drug product as listed in the drug product specification (for example, average weight, hardness, and disintegration properties of the tablet). To ensure batch to batch consistency and control the possible variations in drug product quality, provide applicable (b) (4)

(b) (4)

4. The proposed disintegration (b) (4) acceptance limit of NMT (b) (4) minutes for 500 mg and 2.5 g strength drug products are not appropriately justified based on the (b) (4) data provided in Registration/Stability/Clinical batches (030L13 and 033L13); typically between (b) (4) for 500 mg strength and between (b) (4) for 2.5 g strengths. Revise the (b) (4) limits for disintegration test for the drug products accordingly, to ensure final drug product performance.
5. With regard to ensuring the physical properties of an effervescent tablet for oral solution (hardness, friability and appearance), we have the requests for information.

a.

(b) (4)

b.

c.

6. Provide details on (b) (4) to include in Module 3.2.P.3.3. Provide any studies performed to justify the selection of (b) (4) and to ensure the quality of final drug product.

If you have any questions, please contact Heather Strandberg, Senior Regulatory Health Project Manager, at (240) 402-9096.

Sincerely,

Hitesh Shroff
Division of New Drug Products II/ONDP
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

**Hitesh N.
Shroff -S**

Digitally signed by Hitesh N. Shroff -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000348333, cn=Hitesh N. Shroff -S
Date: 2015.06.20 10:13:22 -04'00'



NDA 207916

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Arbor Pharmaceuticals, LLC
Attention: Allison Lowry
Director, Regulatory Affairs
6 Concourse Parkway
Suite 1800
Atlanta, GA 30328

Dear Ms. Lowry:

Please refer to your New Drug Application (NDA) dated March 30, 2015, received March 30, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Cetylev (acetylcysteine) effervescent tablets, 500mg and 2g.

We also refer to your amendments dated April 1, 2015, April 10, 2015, April 27, 2015 and May 27, 2015.

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 January 30, 2016.

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 postmarketing commitment requests by December 30, 2015. We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information by June 12, 2015:

1. We advised you in the January 29, 2013 pre-IND meeting to use an ANDA product ^{(b) (4)} in the Orange Book as the comparator in bridging studies because the innovator product you are relying on (NDA 13601 Mucomyst) has been discontinued. We also stated it would be acceptable to use ANDA 72,324 as a therapeutic equivalent (AN). Provide a rationale for using a non-RLD ANDA product, ANDA 203853, from Innopharma for your bridging study. ^{(b) (4)}

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified labeling issues that will require more in-depth assessment before we can provide labeling comments or questions. We will request labeling edits as the review team proceeds with their review.

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.

We acknowledge your request for a waiver of the requirement that the Highlights of Prescribing Information be limited to no more than one-half page. We will consider your request during labeling discussions.

REQUIRED PEDIATRIC ASSESSMENTS

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

Because the drug for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call CDR Anissa Davis-Williams, Senior Regulatory Project Manager, at (301) 796-5016.

Sincerely,

{See appended electronic signature page}

Andrew E. Mulberg, M.D., F.A.A.P., C.P.I.
Deputy Director
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

ANDREW E MULBERG
05/29/2015

Davis, Anissa

From: Davis, Anissa
Sent: Wednesday, May 06, 2015 6:05 PM
To: Allison Lowry (ALowry@arborpharma.com)
Subject: NDA 207916 (acetylcysteine) effervescent tablets: Clinical Information Request

We refer to your New Drug Application (NDA) 207916 Cetylev (acetylcysteine) effervescent tablets, submitted on March 30, 2015 pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA).

We are reviewing your application and have the following clinical information request:

- Please either submit the “coding dictionary” for your BA trial or clarify the location in the application.
 - The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

Please respond by May 29, 2015.

Thank you!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

CDR, United States Public Health Service (USPHS)

Senior Regulatory Project Manager

Food and Drug Administration

Center for Drug Evaluation and Research

White Oak Building 22 Room: 5378

10903 New Hampshire Avenue

Silver Spring, Maryland

*Use zip code **20903** if shipping via United States Postal Service (USPS)*

(301) 796-5016 (office)

(301) 796-9904 (fax)

Anissa.Davis@fda.hhs.gov

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/s/

ANISSA A DAVIS
05/06/2015



NDA 207916

NDA ACKNOWLEDGMENT

Arbor Pharmaceuticals, LLC
Attention: Allison Lowry
Director, Regulatory Affairs
6 Concourse Parkway
Suite 1800
Atlanta, GA 30328

Dear Ms. Lowry:

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

Name of Drug Product: Acetylcysteine Effervescent Tablets, 500 mg and 2.5 g

Date of Application: March 30, 2015

Date of Receipt: March 30, 2015

Our Reference Number: NDA 207916

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 May 29, 2015, in accordance with 21 CFR 314.101(a).

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

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

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

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

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

If you have any questions, call CDR Anissa Davis-Williams, Senior Regulatory Project Manager, at (301) 796-5016.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

ANISSA A DAVIS
04/02/2015

BRIAN K STRONGIN
04/08/2015



PIND 116902

MEETING MINUTES

Arbor Pharmaceuticals, Inc.
Attention: Ruth E. Stevens, PhD, MBA
Chief Scientific Officer, Camargo Pharmaceutical Services, LLC
9825 Kenwood Road, Suite 203
Cincinnati, OH 45242-6252

Dear Dr. Stevens:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Acetylcysteine Effervescent Tablets for Oral Solution.

We also refer to the meeting between representatives of your firm and the FDA on January 29, 2013. The purpose of the meeting was to discuss the development plans for Acetylcysteine Effervescent Tablets for Oral Solution.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

Jessica M. Benjamin
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn
Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-IND

Meeting Date and Time: January 29, 2013 from 12:00 PM to 1:00 PM EST
Meeting Location: White Oak Building 22, Conference Room: 1421

Application Number: PIND 116902
Product Name: acetylcysteine effervescent tablets for oral solution
Indication: To prevent or lessen hepatic injury [REDACTED] (b) (4)
[REDACTED] ingestion of a potentially hepatotoxic quantity of acetaminophen

Sponsor/Applicant Name: Arbor Pharmaceuticals, Inc.

Meeting Chair: Ruyi He, MD
Meeting Recorder: Jessica M. Benjamin, MPH

FDA ATTENDEES

Andrew Mulberg, MD, FAAP, CPI, Deputy Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Ruyi He, MD, Clinical Team Leader, DGIEP
Lara Dimick, MD, Clinical Team Leader, DGIEP
David Joseph, PhD, Lead Interdisciplinary Scientist, DGIEP
Yuk-Chow Ng, PhD, Pharmacologist, DGIEP
Kristine Estes, PhD, Clinical Pharmacology Reviewer, Office of Clinical Pharmacology
Mike Welch, PhD, Biostatistician Team Leader, Office of Biostatistics
Behrang Vali, MS, Biostatistician, Office of Biostatistics
Marie Kowblansky, PhD, CMC Lead, Office of New Drug Quality Assessment
Jessica Benjamin, MPH, Senior Regulatory Project Manager, DGIEP
Maria Walsh, Associate Director of Regulatory Affairs, ODE III

SPONSOR ATTENDEES

Laurence J. Downey, MD, VP Medical and Scientific Affairs, Arbor Pharmaceuticals
Adel Gomez, Director, Manufacturing and Validation, Arbor Pharmaceuticals
Allison Lowry, Director, Regulatory Affairs, Arbor Pharmaceuticals

[REDACTED] (b) (4)

1.0 BACKGROUND

Arbor Pharmaceuticals plans to submit a New Drug Application (NDA) via the 505(b)(2) regulatory pathway for its proposed Acetylcysteine Effervescent Tablets for Oral Solution product (2.5 and 0.5 g strengths) to prevent or lessen hepatic injury (b) (4) ingestion of a potentially hepatotoxic quantity of acetaminophen. The proposed product's labeling will be consistent with the currently approved product's labeling, with the exception of the dosage form and directions for preparation and administration. The proposed Acetylcysteine Effervescent Tablets for Oral Solution product is only seeking the (b) (4) indication.

Each of Arbor Pharmaceutical's questions is presented below in italics, followed by the Division's response in bold. A record of the discussion that occurred during the meeting is presented in normal font. The Division provided preliminary written responses to the sponsor on January 25, 2013.

2. DISCUSSION

Question 1. Is the Agency in agreement with the 505(b)(2) regulatory pathway for the Acetylcysteine Effervescent Tablets for Oral Solution product?

FDA Response:

Yes the 505(b)(2) pathway is acceptable.

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry Applications Covered by Section 505(b)(2)" (available at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079345.pdf>.

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 available at

<http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf>).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, 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). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

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 literature reports must be included in the application and any proprietary names in those reports identified. If a product is identified by proprietary name and the information in the literature report is required for approval, including for the labeling, then that product must be included in the list of products relied upon for approval and the required patent notification and certification procedures followed.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on the Agency's finding of safety and/or effectiveness for a listed drug or published literature.

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s), you should identify each listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

Discussion:

There was no further discussion of this point.

Question 2. Does the Agency agree that [REDACTED] (b) (4) on which to rely for Arbor's acetylcysteine product is Acetylcysteine Solution; Inhalation, Oral 20% (ANDA [REDACTED] (b) (4))?

FDA Response:

No, we do not agree. While it is appropriate to use the ANDA product [REDACTED] (b) (4) in the Orange Book as the comparator in bridging studies when the innovator product has been discontinued, you will need to identify the NDA product (i.e., Mucomyst) that was the basis for submission of the ANDA product as the listed drug relied upon to support your proposed 505(b)(2) application. You must also provide a patent certification or statement with respect to each patent listed in the Orange Book for the listed drug upon which you rely (see 21 CFR 314.54(a)(1)(vi)). Note also that reliance on FDA's finding of safety and/or effectiveness for a discontinued listed drug is contingent on FDA's finding that the drug was not discontinued for reasons of safety or effectiveness.

Discussion:

Arbor will rely on Mucomyst, NDA 13601, but will use an ANDA in comparator studies. Arbor will conduct a patent certification to provide supportive evidence that Mucomyst was not withdrawn for reasons of safety and efficacy. Arbor acknowledges that the FDA will make the final determination during the NDA review.

Question 3. Acetylcysteine inhalation solution [REDACTED] (b) (4) [REDACTED] does the Agency find it

acceptable that Arbor used Acetylcysteine Solution; Inhalation, Oral 20% (ANDA 72-324; Bedford Laboratories, manufactured for Roxane Laboratories, Inc.), an AN (therapeutic equivalent code for solutions and powders for aerosolization) rated product, as marketed equivalent of the LD, in the planned in vitro comparison testing?

FDA Response:

Yes, we agree. See response to Question 2 above as well.

Discussion:

There was no further discussion of this point.

Question 4. Arbor intends to submit a request for Orphan Drug Designation for the Acetylcysteine Effervescent Tablets for Oral Solution product as an antidote to prevent or lessen hepatic injury [REDACTED] (b) (4) ingestion of a potentially hepatotoxic quantity of acetaminophen. Does the Agency agree with Arbor's plan to submit a request for orphan drug designation for the Acetylcysteine Effervescent Tablets for Oral Solution product?

FDA Response:

The Agency has no objection to your submitting an Orphan Drug Designation Application.

Discussion:

There was no further discussion of this point.

Question 5. Arbor plans to submit a request for Orphan Drug Designation for the Acetylcysteine Effervescent Tablets for Oral Solution product for the treatment of acetaminophen overdose. The requirements of PREA will not applicable if orphan drug designation is granted. Does the Agency concur?

FDA Response:

If Orphan Drug Designation has been granted at the time of NDA submission, you will be exempt from PREA requirements. If Orphan Drug Designation has not been granted at the time of NDA submission, you will need to meet PREA requirements.

Discussion:

Arbor will submit a PREA plan in advance of the NDA submission, if Orphan Drug designation has not been granted. Dr. Dimick will send Arbor references to the published literature on the approval history for acetylcysteine. Arbor will contact PMHS for advice on appropriate timing of the submission of the PREA plan.

Question 6. Assuming that the Arbor product has equivalent acetylcysteine content (based on the information for use in the LD package insert) and the excipients have been established as safe and they do not alter the dissolution profile, does the Agency agree that Arbor's acetylcysteine product is eligible for a BA/BE waiver?

FDA Response:

No we do not agree. As per 21 CFR 320.21(1) and §320.21(2), you are required to include in your NDA submission, either evidence of measuring the in vivo bioavailability (BA) or bioequivalence (BE) of the drug product that is the subject of the NDA or information to permit FDA to waive the submission of evidence measuring in vivo bioavailability or bioequivalence. To satisfy the CFR's BA/BE evidence requirement, you may include in your NDA:

- **The drug product specific BA/BE study**

or

- **Pharmacokinetic literature data, in lieu of the drug product specific BA studies. However, FDA's acceptance of the provided literature information/data as evidence of satisfying the BA requirement is contingent on the appropriateness of the scientific bridge between the formulation used in the literature studies using the oral route of administration and your proposed formulation.**

or

- **Information supporting a BE waiver request. For the biowaiver you should demonstrate that your proposed drug product is a true solution and contains an active drug ingredient in the same concentration and dosage form as a drug product that is the subject of an approved full new drug application or abbreviated new drug application; and contains no inactive ingredient or other change in formulation from the drug product that is the subject of the approved full new drug application or abbreviated new drug application that may significantly affect absorption of the active drug.**

The adequacy of the submitted information to support BA/BE, clinical, and, labeling decisions is a review issue under the NDA.

Discussion:

The Division stated that it is sufficient to use HPLC, or some other appropriate analytical technique, to demonstrate a true solution at a specified time. The Arbor product, acetylcysteine concentration, is at or below the listed drug concentration of 5%, secondary to Arbor using a consistent volume to reduce dosing error. The FDA finds this acceptable to meet the requirements of 21 CFR 320.21(1) and §320.21(2). Arbor will provide data based justification to demonstrate that each inactive will not impact absorption of the active drug. The Division has agreed that Arbor may submit this justification under the IND for review, prior to the NDA submission.

Question 7. Does the Agency agree that clinical studies are not required?

FDA Response:

If BA/BE is established or a biowaver is granted between your product and the comparator product and no safety concern on the excipients from nonclinical, additional clinical studies may not be needed. Please see response to Question 8.

Discussion:

There was no further discussion of this point.

Question 8. Does the Agency agree that nonclinical studies are not required?

FDA Response:

We disagree with your approach in evaluating the safety of the excipients. Safety evaluation of the excipients should be based on maximum daily intake, not on a per tablet basis. For example, a patient weighing 60 kg will ingest 14 high strength (2.5 g) tablets during the first day of treatment, when the maximum daily dose is administered. Based on our safety assessment using this approach, we do not have concerns regarding the following excipients: sodium bicarbonate, maltodextrin, sucralose, sodium benzoate, and (b) (4). However, we have concerns/comments regarding the lemon and peppermint flavors.

Regarding the peppermint flavor, the maximum daily intake will be (b) (4) mg (based on a 60-kg bodyweight), which exceeds the maximum potency of 11 mg in the FDA inactive ingredients database. To address our concerns, you first need to identify the type and/or composition of the peppermint flavor used in your product. A GRAS designation by FEMA (Flavor and Extract Manufacturers Association) is acceptable as evidence of safety of the flavor. If no applicable regulatory information or other safety information from public health authorities is available for your selected flavor, you will need to provide toxicity information. Original full reports of toxicity studies or published toxicity studies of the flavor may be submitted to demonstrate safety of the flavor. Toxicity information may be available for individual flavoring agents in a DMF. You will need to provide a letter of authorization from the DMF holder before we can review any information in the DMF. If none of the above information is available, either you or the DMF holder will need to provide safety information on the individual ingredients in the flavor. If neither the regulatory nor toxicity information on your selected flavor or the individual ingredients is adequate to assure safety for your proposed product, you may need to conduct nonclinical safety studies.

Regarding the lemon flavor, the maximum daily intake will be (b) (4) mg (based on a 60-kg bodyweight), which exceeds the maximum potency of 340 mg in the FDA inactive ingredient list. In addition, it is unclear whether the flavor in your product is identical to the one cited, i.e. (b) (4). You need to provide safety information as described above for the peppermint flavor.

Discussion:

In the event that it is required, FDA referred Arbor to the FDA guidance on the nonclinical development of excipients for detailed information on potential nonclinical studies for the flavors.

Question 9. The proposed release and stability specifications for the Arbor effervescent tablets for oral solution are listed in Table 22 of the background package. Does the agency agree that these are acceptable release and stability specifications for the commercial product?

FDA Response:

Based on the information in your briefing package, your proposed specification is reasonable. However, it will be reevaluated in the context of your full NDA submission.

Discussion:

There was no further discussion of this point.

Question 10. Arbor plans to submit six months of real-time and accelerated stability data generated on its pivotal batches at the time of filing the 505(b)(2) application and then provide supplemental stability data during the review cycle. Does the Agency find this acceptable?

FDA Response:

No, you will need to submit twelve months of stability data at the time of NDA submission. Additional stability data will only be accepted up to 30 days after the initial submission. Adherence to this schedule is critical for us to meet all PDUFA and GRMP timelines.

Discussion:

FDA policy will be reevaluated in view of the current drug shortage and/or possible orphan drug designation. The final decision will be communicated to Arbor as an addendum to the meeting minutes.

Post-Meeting Note:

For the indication that you are seeking, your proposed product is not in shortage. Therefore, you will need to submit twelve months of stability data, as indicated in our initial response.

ADDITIONAL COMMENTS:

Please provide the following for each additional clinical study you plan to include in your eventual 505(b)(2) NDA submission:

1. All clean/locked clinical data presented in electronic datasets, submitted utilizing SAS Version 5 Transport, along with the annotated case report form (aCRF) and a thorough data definition file. We recommend that the electronic datasets, aCRF, and data definition

file comply with the latest CDISC/SDTM, CDISC/CDASH, and CDISC/Define.XML standards respectively. Define.PDF is also an acceptable format for the data definition file.

2. All corresponding analysis data presented in electronic datasets, submitted utilizing SAS Version 5 Transport, along with a thorough data definition file. We recommend that these electronic datasets incorporate the modeling approaches described by the latest CDISC/ADaM standard along with both the CDER Data Standards Common Issues Document and the Study Data Specifications document (<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>). We recommend that the data definition file comply with the latest CDISC/Define.XML standard, however Define.PDF is also acceptable.

3. A well commented and organized software program written for each analysis dataset and efficacy table created.

3.0 PREA REQUIREMENTS

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting occurred prior to November 6, 2012 or an EOP2 meeting will not occur, then:

- if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).
- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP, including a PSP Template, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items from this meeting.

6.0 ATTACHMENTS AND HANDOUTS

There were no handouts for this meeting.

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/s/

JESSICA M BENJAMIN
02/27/2013